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OF
THE JOHNS HOPKINS HOSPITAL

(THE PUBLICATION OF THE MEDICAL SCHOOL AND HOSPITAL)

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William Sydney Thayer

UNIV. OF MICH.

William Sydney Thayer

June 23, 1864–December 10, 1932

Dr. William Sydney Thayer was born in Milton, Massachusetts, on June 23, 1864. His forebears representing the best of the inheritances and traditions of the early New England character, he grew up in an environment of scholarly interests of the highest type. Educated at private schools and the Cambridge High School, he entered Harvard College, graduating with the class of 1885. Four years later he received his Medical Degree from the Harvard Medical School. The two following years were spent as house officer at the Massachusetts General Hospital in Boston.

In November 1890 he came to Baltimore as Dr. Osler's Second Assistant on the resident Medical Staff in the Johns Hopkins Hospital. In September 1891, he was appointed Resident Physician, and held this position for seven years. He also served as Dr. Osler's first assistant with the rank of Associate Professor, up to the time of Dr. Osler's resignation in 1905. He was appointed Professor of Clinical Medicine in this year and in 1918 succeeded to the Chair of Medicine in the Johns Hopkins University and became Physician-in-chief to the Johns Hopkins Hospital. This position he held until 1921 when he withdrew from the Professorship of Medicine. His resignation at this time illustrates in a singular way his innate character and his spirit of unselfishness, believing as he did that he should make way for a younger man. Fortunately for us he maintained his connection with the hospital and the student body as Professor Emeritus, carrying on with all his rare enthusiasm and sharing constantly with his colleagues and associates from his great store of clinical knowledge, teaching both by precept and example.

During the War he was appointed Chief Medical Consultant of the United States Expeditionary Forces in France with the rank of Brigadier General. In 1927 he was elected to the Presidency of the American Medical Association and gave unstintedly of his time and strength to the welfare of the Association during his year of office.

He had been for many years a member of the Harvard University Board of Overseers and was always keenly devoted to the interests of his Alma Mater in a way that represented a characteristically loyal affection for the Cambridge University. He was also a vice-president of the Harvard Alumni Association. His membership in foreign and American Societies comprised a unique list of distinguished bodies that sought to do him honour. He was an LL.D of Edinburgh University, 1927, Honorary member of the Therapeutical Society of Moscow, 1897, Honorary member of the Royal Society of Medicine of Budapest, 1909, Membre associé étranger de l'Académie de médecine, Paris, 1918, Membre associé étranger de la Société Royale des sciences médicales et naturelles de Bruxelles, 1919, Honorary Fellow of the Royal Society of Medicine, London, 1923, Honorary member of the Association of Physicians of Great Britain and Ireland, 1925, Honorary Fellow of the New York Academy of Medicine, 1926, Member of the American Philosophical Society, 1924, and Fellow of the American Academy of Arts and Sciences, 1921. In 1927 a group of friends gave to the University a fund to establish an endowment to be known as the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine, as a signal mark of their appreciation of his achievements and a tribute to the memory of his wife, whose devotion to all his interests played so important a part in his life. Mrs. Thayer's death during Dr. Thayer's absence in Russia in 1917 on the American Red Cross Mission, tragic as the circumstances were, was met by him with the same unfailing courage and fortitude with which he faced the lesser tragedies of life.

In the death of Dr. Thayer the Johns Hopkins Hospital, the University and we, his associates, have suffered an irreparable loss. Though he had realized for many months certain warnings, and by no one had their implication been more keenly understood than by Dr. Thayer, yet throughout these months he had carried himself with all the old accustomed buoyancy and cheerfulness, with no selfish thoughts, always thinking of the other individual and what he could do to mitigate distress of body and mind, the purpose to which he had so unselfishly devoted his life, guided always by the highest ideals.

We have emphasized our sense of personal loss, but his death leaves an emptiness which it is difficult to appraise, and takes from

the world at large one whose influence was far reaching in a multitude of varied activities. His public achievements in behalf of Medicine in this country and abroad are too well known to need comment. His influence upon clinical medicine in an academic sense was equalled by few and surpassed by none. The host of individuals who have gone forth from this his old clinic as "Transmuters, Transmitters, and even as Creators," bears witness to the widespread influence of his teaching and example.

It would be far beyond the limits of this brief note to sketch even in outline the many-sided accomplishments of Dr. Thayer's extraordinary versatility, his interests in Science generally, in Music, Art and Literature, and what, for lack of a better word, might be called his appreciation of the Humanities. This outstanding quality of his character was so well illustrated by his interest in, and devotion to, not only Russian literature but to the people of Russia even before the débâcle and particularly to the children of Russia after it. His interest in the Russian language had its inception in 1895 and never flagged, for he continued in its pursuit until the end and his translations from the Russian poets published in his volume of verse "America 1917" are charmingly done. Of his public addresses, as the Essayist of the occasion, one cannot forbear recalling that upon Pasteur—The Contributions of Pasteur to Medicine and Humanity—delivered at the Sorbonne, May 22nd, 1923, in French, before a crowded theatre and received with tremendous acclaim, and that upon Richard Bright, delivered at Guy's Hospital, London, July 8, 1927, on the occasion of the Bright Centenary celebration, both finished essays done with all the gift of expression so peculiarly his.

Of his many contributions to Medical Science may we allude to the early papers upon malaria and particularly to the exhaustive monograph upon the Malarial Fevers of Baltimore, to his work upon bacterial endocarditis culminating in the monograph which appeared in the Johns Hopkins Hospital Reports in 1916, to the early studies upon gonococcal endocarditis which did so much to clear the way to a better understanding of many an obscure problem in clinical medicine; to his studies upon typhoid fever both clinical and pathological, his early contributions to the diseases of the blood at a time when our knowledge was far less exhaustive than it is today. His contributions

to disease of the pancreas, to trichinosis, to the subject of hypertrophic pulmonary osteo-arthropathy and his studies upon cardio-vascular disease in all its phases have all added to our knowledge of disease processes. Among his many delightful essays not wholly medical in their theme, reference should be made to the one upon Cotton Mather's Rules of Health, which appeared in the Bulletin in September, 1905.

This is but a list of a few of his important contributions chosen to emphasize the immense catholicity of his interests. His collected reprints up to the year 1932 include 179 titles covering every field of medical knowledge.

Of his charming personality it is difficult indeed to express adequately a just appreciation of the many-sided qualities of the man which so endeared him to his fellows. His sense of honour and justice, his deep human sympathy, his never failing ability to see the good in every individual, and his blindness to the evil or to human weakness, were outstanding; his spirit of charity towards all was magnificent. Added to this was a most delightful sense of humour. Many an awkward situation was saved by his graceful turn of the jarring note by some amusing anecdote or parry, recounted as only he could tell it.

No account of Dr. Thayer's many-sided character could be complete or do him full justice that did not allude, if even only by suggestion, to his appreciation of what we may term the formalities of every-day living, a part of his make-up that stood out in striking contrast to the present-day informality. It was all as much a part of the very essence of the man as was his love of the very best in art or literature.

The most gracious of men he was inspired by a rare generosity, and the sweetness of his nature and the simplicity of his character were beyond measure. His going was for him after all the simplest way. His life was complete and he died as he had lived peacefully with an attitude of extraordinary resignation that his task was finished. To us his death leaves a void that cannot be filled. We shall never know his like again.

E. P. C.

THE PATHOGENESIS OF TUBERCULOUS MENINGITIS

ARNOLD R. RICH AND HOWARD A. McCORDOCK

From the Department of Pathology, Johns Hopkins Medical School, Baltimore, Md.

Acute diffuse tuberculous meningitis is characterized especially by its exudative inflammatory nature, and by the tendency to widespread necrosis of the inflammatory exudate and of contiguous meningeal tissues. Even in cases in which the duration has been sufficiently long to permit the appearance of a proliferative reaction leading to the formation of true tubercles or of a compact tissue composed of epithelioid cells and fibroblasts, one usually finds the remains of an earlier exudative-necrotic process. Since extensive exudative inflammatory reactions with prominent necrosis in tuberculosis are well known to be expressions of the allergic state, and since tuberculous meningitis develops only in persons carrying an older sensitizing infection somewhere in the body, it is proper to regard these characteristics of acute tuberculous meningitis as having been determined by allergy. The problem which we wish to discuss in this paper is the mechanism by which tubercle bacilli are deposited in the meninges in numbers sufficient to call forth so violent an allergic reaction.

If one turns for information to leading textbooks and to the literature, it will be found that, while it is mentioned that meningitis may in certain cases result from the extension of tuberculous infection from a focus situated within the brain, or within the bones which enclose the the central nervous system, most cases are regarded as the result of direct meningeal infection by way of the blood stream, appearing usually as a part of the widespread dissemination of bacilli throughout the body during the septicaemia responsible for miliary tuberculosis. This attitude is, without doubt, a result of the observation of the frequent coincidence of tuberculous meningitis and miliary tuberculosis, especially in infants, together with the fact that the demonstration of an older, adjacent tuberculous focus as the source of the meningeal infection has been decidedly exceptional in any routine series of cases.

It is, therefore, universally assumed without hesitation that tubercle bacilli circulating in the blood stream can readily lodge in the meninges in numbers sufficient to call forth the familiar diffuse inflammatory-necrotic reaction.

There are, however, several circumstances which should disturb the easy acceptance of the idea that the meninges can be readily infected so heavily with tubercle bacilli by way of the blood stream, and that tuberculous meningitis is, commonly, merely a part of generalized miliary tuberculosis. In the first place, it is a quite familiar fact that meningitis may be absent in the most extreme cases of miliary tuberculosis in which every susceptible organ is riddled with tubercles; and we have seen this occur in individuals who had a high degree of allergy, as determined by graded tuberculin tests, during the course of the miliary tuberculosis.

In the second place, we have frequently observed that the age and character of the miliary tubercles in the viscera in patients dying with miliary tuberculosis and tuberculous meningitis may not correspond at all with the age or character of the meningitis—a point which speaks strongly against the contemporaneous origin of the meningitis and the miliary tuberculosis. In some cases the visceral tubercles are clearly much older than the fresh meningitis, while in other cases only minute fresh tubercles are found in the viscera in association with a chronic, fibrous meningitis.

In the third place, there are many cases in which meningitis occurs in the complete absence of miliary tuberculosis. It is, of course, in these cases especially that one would postulate the existence of a nearby, older tuberculous lesion from which the infection extended directly to the meninges, but it is important for the present consideration that the records of our department contain numerous instances of this sort in which no older adjacent lesion was found at autopsy, and, without doubt, this situation has been encountered in almost every autopsy service.

Finally, it may be recalled that the various tissues react in a remarkably constant manner to a blood-stream infection with the tubercle bacillus. The spleen, lungs, bone-marrow and liver are the organs chiefly affected, and if miliary tubercles are found anywhere following a general dissemination of bacilli, one can confidently expect to find

them more numerous in these tissues than in others such as the pancreas, the thyroid, the muscles, etc., which are noted for their relative freedom from involvement as a result of blood-stream infection. It never happens that the spleen or the lungs, for example, are spared when the rest of the organs are peppered with miliary tubercles; nor does it happen that the pancreas is found riddled with tubercles when the more susceptible organs contain relatively few. It seems rather curious, therefore, that the meninges should be such exceptional tissues that no one hesitates to state (1) that they are frequently heavily infected by way of the blood stream during miliary tuberculosis; (2) that they are not infrequently completely spared during the most extreme miliary tuberculosis; and (3) that they may be heavily infected by way of the blood stream during miliary tuberculosis even when the most susceptible tissues contain only a few scattered tubercles.

In connection with the fact that extreme miliary tuberculosis may occur without meningitis, an examination of the literature will convince one that the experimental injection of even massive doses of tubercle bacilli into the blood stream, while causing a severe generalized miliary tuberculosis, nevertheless has not produced a simultaneous acute, exudative meningitis; indeed, not even when actual emboli of bacilli were introduced directly into the carotid artery. Tuberculous meningitis has been produced at will experimentally by a few investigators, but direct infection of the meninges had always to be performed in order to produce the desired lesion. The immediate effect of infection by way of the blood stream has been only rare, discrete tubercles in the meninges. As long ago as 1898 Péron (1), one of the earliest to study tuberculous meningitis experimentally, wrote after unsuccessful attempts to produce the lesion by injecting bacilli directly into the carotid artery: "*On ne peut réproduire la méningite tuberculeuse que par l'injection de liquides virulents dans la cavité arachnoïdienne.*" This was the experience of Armand-DeLille in 1903 (3), and of Fieandt (4) in his extensive investigation in 1910. Both of the latter workers injected into the carotid artery of the dog emboli of bacilli large enough to produce small meningeal haemorrhages and areas of encephalomalacia, but they failed to produce any lesion in the meninges except sparsely scattered minute, discrete tubercles. Other investigators have used different animals and different suspensions of bacilli with the same

result. On the other hand, no one has experienced the slightest difficulty in producing typical diffuse tuberculous meningitis if the bacilli were introduced directly into the subarachnoid space (Martin (5), Péron (1), Sicard (6), Richet and Roux (7), Manwaring (8), Austrian (9), Soper and Dworski (10)).

Since acute tuberculous meningitis in the human being has clearly the characteristics of an allergic reaction, and since we know well from all experimental evidence that such extensive allergic reactions cannot be initiated by a few bacilli, we may legitimately enquire whether it is to be expected that great numbers of bacilli will be deposited in the meninges during the septicaemia of miliary tuberculosis. All experimental work points to the contrary. Aside from the several direct attempts to produce tuberculous meningitis by blood-stream infection, innumerable investigators during many years have for different reasons injected tubercle bacilli, in large and in small doses, into the blood stream of normal and of allergic laboratory animals. The results, as far as the production of prompt, acute meningitis is concerned, have not necessitated any revision of the conclusion of Péron which we have quoted above. The distribution of tubercles in miliary tuberculosis follows very closely, indeed, the early distribution of inert particulate matter introduced into the blood stream, and it has been shown by Brickner (11), in this laboratory, that the pia-arachnoid must be grouped with such tissues as the heart, the pancreas and the thyroid which stop and hold only relatively minute amounts of any circulating, particulate material. But even if, during blood-stream infection, tubercle bacilli did lodge in the meninges in scattered foci as readily as they do in other organs, one would expect at most only a small local reaction with subsequent discrete tubercle formation at each site where one or several bacilli lodged, rather than the extensive, diffuse exudation with necrosis which characterizes tuberculous meningitis. As a matter of fact, in the cases of extreme miliary tuberculosis without diffuse meningitis, minute search will usually reveal a few sparsely scattered tubercles in the meninges of the same general size and character as those found in the viscera (Figs. 19, 20, 21 and 22), but for the production of a diffuse, acute, inflammatory-necrotic tuberculous reaction, really considerable numbers of bacilli, or necrotic tissue saturated with their products, must be discharged into the meningeal

spaces. The conditions responsible for the occurrence of an extensive tuberculous inflammatory effusion into the subarachnoid space are quite the same as those necessary for similar reactions in the serous cavities, for they are merely the general conditions governing extensive inflammations in tuberculosis. The pleura, peritoneum and pericardium stop and hold very little of any inert particulate matter injected into the circulation, and they are correspondingly little affected during miliary tuberculosis. Experimentally, no one has been able to produce an exudative inflammation in these cavities by injecting tubercle bacilli into the blood stream of normal or of allergic animals. Indeed, Paterson (12) found it necessary not only to introduce the bacilli directly into the pleural cavity of an allergic animal, but to introduce, suddenly, "huge masses of bacilli" in order to call forth an outspoken reaction of this type.

It must be remembered that the tubercle bacillus differs from ordinary pyogenic bacteria in its much more sluggish rate of reproduction. Several pneumococci, for example, deposited in the meninges of a susceptible animal, proliferate so vigorously that thousands or, indeed, millions will be present at the site after the lapse of a few hours. It is not to be wondered at, therefore, that meningitis can be produced more readily by the intravenous injection of pyogenic bacteria. Not so in the case of the tubercle bacillus, however, which proliferates so slowly that if only several bacilli are deposited at any one site they will be enclosed by tubercle formation before any appreciable multiplication has taken place.

These considerations, together with the fact that we had never seen exudative meningitis develop as an *immediate and direct* result of the many intravenous inoculations which we have performed during the course of a more general investigation into the pathology of tuberculosis in which we were engaged during several years (13), led us to subject to a critical examination the widely accepted view that tuberculous meningitis is commonly the result of direct, haematogenous infection of the meninges during the course of miliary tuberculosis.

EXPERIMENTAL STUDIES

We approached the problem first by experiment. Since the investigators who attempted infection of the meninges by way of the blood

stream used only normal, non-allergic animals, and since the studies of other investigators on the general effect of intravascular *reinfection* have not been directly concerned with the problem before us, we wished to know at the outset whether or not bacilli introduced into the blood stream of an allergic animal would tend to lodge in the meninges, or to escape into the subarachnoid space, in numbers sufficient to cause exudative meningitis. Our first material for the study of this point comprises a series of 20 allergic animals and 20 non-allergic, normal controls. Half of these animals were rabbits, and half guinea-pigs. The rabbits were sensitized by subcutaneous inoculation with the H37 human strain, and the guinea-pigs with the R1 human strain of low virulence. All animals of the allergic group gave strongly positive skin reactions to 5 mg. of tuberculin before being used for the experiment. Large doses of virulent bovine (B1) bacilli were then injected intravenously into the rabbits; the guinea-pigs received injections of heavy suspensions of the virulent H37 human bacillus. Animals were killed at weekly intervals during six weeks. Although all of the animals at autopsy had more or less extensive visceral miliary tuberculosis, the gross and microscopic study of the meninges showed that in only two animals out of the forty did anything develop even remotely suggestive of exudative meningitis. The lesion in these animals consisted only in the presence of a fresh scattering of mononuclear cells in the subarachnoid space. We shall discuss below the origin of this slight meningeal involvement and show that it was not a result of direct haematogenous infection of the meninges.

In another experiment, two highly allergic rabbits and two normal controls were given repeated intravenous injections of 2 cc. of a cloudy suspension of B1 bacilli (bovine). The injections were given on November twenty-third, December fourth and December twelfth. One of the allergic animals died on December tenth, six days after the second injection and seventeen days after the first. The other allergic animal died two days after the third injection and twenty-one days after the first. The control rabbits died, respectively, nine and eleven days after the third injection, or twenty-eight and thirty days after the first injection. Tuberculin tests carried out every four days during the experiment showed that both of the originally allergic rabbits failed to react to 5 mg. O.T. during the week pre-

ceding death. Up to this time they had reacted strongly to this amount of tuberculin. Both of originally normal animals began to react to 5 mg. O.T. sixteen days after the first intravenous injection. One of these rabbits maintained a high degree of reactivity during the rest of the experiment. The other showed some decrease in reactivity following the third injection and failed to react two days before death. At autopsy all four animals had an extreme visceral miliary tuberculosis; no meningitis was found, however, grossly or microscopically, in any of them.

Finally, in order to increase still further the chance of meningeal infection, we injected 4.5 cc. of a cloudy suspension of virulent bovine (B1) bacilli directly into the carotid artery of each of two allergic and two normal rabbits. An allergic animal and a control were killed at the end of two and five days following the injection. The meninges of all were normal grossly and microscopically. We likewise injected 1.5 cc. of a heavy suspension of virulent human bacilli (H37) into the carotid artery of each of three allergic and three normal guinea-pigs. An allergic and a control animal were killed at the end of two days, fourteen days, and twenty-eight days following the injection. Except for rare minute, discrete tubercles, the meninges of all were normal grossly and microscopically. The viscera of the animals surviving five days or more contained many miliary tubercles.

Thus, out of fifty-four animals, half of which were allergic, in no instance did a diffuse exudative meningitis follow directly the intravascular injection of large numbers of tubercule bacilli. It seemed quite clear to us, therefore, that, in the rabbit and guinea-pig at least, circulating bacilli do not tend to stop in the meninges in numbers sufficient to call forth that type of reaction. That the same thing must be true in the case of the human being seems obvious from the many cases of extreme generalized miliary tuberculosis without meningitis. We did, however, frequently find small circumscribed tubercles in the brain substance, more rarely in the meninges, and several times we found tuberculosis of the choroid coat of the eye. It was in association with an extensive tuberculosis of the eye that we found the early meningitis in one of the two animals mentioned above. Neither of these rabbits was allergic at the time of the intravenous injection, and neither was killed until six weeks had elapsed following the injection.

It is, therefore, clear that the few fresh mononuclear cells which were present in the meshes of the pia-arachnoid without a trace of any other meningeal lesion could hardly have been a direct and immediate response to the intravascular injection made six weeks previously. In the animal in which we found a tuberculous destruction of the choroid of the eye it is not difficult to understand the origin of this slight and fresh meningeal inflammation, since there is a direct communication between the meninges and the choroid in the rabbit and microscopic study showed clearly the path of backward extension. Unfortunately the eyes were not examined in the case of the other animal, but the mildness and freshness of the process made it clear beyond question that it was a very recent meningeal involvement rather than an immediate effect of the intravascular injection made six weeks previously. The infection must have extended to the meninges from a focus which developed either in the eye or in the brain substance, and this we believe to be the manner of origin of the meningitis which is sometimes found at autopsy some weeks after experimental intravascular injections of bacilli.

In a preliminary report of this work we stated that we were unable to produce meningitis by intravascular injections of bacilli (13). This was perhaps badly stated, for, of course, we have seen meningitis develop weeks after such inoculations. We wished rather to say that we had never been able to produce a prompt meningitis, resulting at once from direct haematogenous meningeal infection and appearing contemporaneously with the miliary tuberculosis caused by the injection; for cases which develop some weeks after the injection are not the direct result of injected bacilli escaping from the blood stream into the meninges, but are rather a later and fortuitous result of the discharge of bacilli from an adjacent tuberculous focus produced by the injection.

We next turned to the direct infection of the meninges, for although, as we have said, various investigators have produced meningitis in this manner, histological descriptions of the lesions have been either very sketchy or, more usually, completely lacking in the reports, and it is important for the present problem to know whether infection by this route can produce the particular vascular lesion which has been interpreted as a proof of the haematogenous origin of the condition.

It is clear from the most cursory histological examination of human tuberculous meningitis that there is a very definite tendency for the infection to be particularly severe in and about the walls of the meningeal arterioles. The intima may be infiltrated with mononuclear cells; the media and adventitia are frequently infected and may become completely caseous; or a perfectly normal vessel may be surrounded by a sheath of inflammatory cells with necrosis which encroaches upon the adventitia only. This vascular involvement is regarded by many as evidence that the bacilli reach the meninges through the walls of the small vessels (14). In our studies of human cases we have not been impressed by these vascular lesions as constituting evidence that the bacilli infected the vessels from within. In the first place one can more easily find instances in which the adventitia is caseous while the media and intima are uninfected than those in which the endothelium is lifted up over an accumulation of cells while the media and adventitia are normal. It is, furthermore, infinitely more easy to find vessels in which the adventitial and medial changes are obviously, by reason of their extent and the presence of necrosis, older than the fresh intimal infiltrations, than it is to find vessels in which the reverse situation is present. Even in vessels in which the intimal involvement seems isolated and oldest, serial sections of the vessel and its proximal branches would be necessary to rule out the extension of the infection from a nearby region in which the entire wall was affected. Hektoen (14) states that he has found instances of intimal infiltrations unassociated with medial or adventitial changes as far as he could determine by serial sections. The occurrence of isolated, direct intimal infection need not be disputed. Since almost every well marked case of tuberculous meningitis will show complete caseation of the walls of blood vessels with the discharge of bacilli into lumina in which fresh, apparently circulating blood is found, it is clear that the meninges soon contain many foci from which bacilli are discharged into the blood, and it is quite reasonable to regard an isolated intimal infection in a meningeal blood vessel as a result of the presence of a discharging focus in a vessel at some distance behind the affected site, subjecting that site to a continued, unusual opportunity for direct blood-stream infection.

Considerations of this nature cast doubt upon the value of the vascu-

lar alterations as evidence of an haematogenous origin of tuberculous meningitis, but it was obviously of major importance to the question to know whether identical vascular lesions would occur when the meninges were infected directly, and the possibility of blood-stream infection excluded. For the purpose of studying this point we infected the meninges directly, by way of the optic foramen. Each of six allergic and six normal rabbits received 1 cc. of an opalescent suspension of B1 (bovine) bacilli, and each of six allergic and six normal guinea pigs received 0.5 cc. of a similar suspension of H37 (human) bacilli. The animals were killed at various intervals between forty-eight hours and twenty-five days following the injections. The chief differences between the histological appearance of the meninges of the allergic animals, as contrasted with those of the controls, consisted in the more prompt appearance of outspoken, exudative inflammatory lesions and of necrosis in the former. In the latter, after an immediate but relatively mild outpouring of inflammatory cells, compact sheets of well-formed epithelioid cells were formed in the spaces of the meninges. Later, as the animals became allergic as a result of the infection, foci of necrosis laden with bacilli appeared in these cell accumulations, and a second exudative inflammation appeared about these foci as bacilli were discharged from them into the now allergic adjacent meninges. The character of the lesions in the originally allergic animals, and in the normals after the infection had rendered them allergic, had all of the distinctive characteristics of human tuberculous meningitis. Inflammatory fluid and cells (predominately mononuclear) filled the meningeal spaces and the familiar necrosis of the exudate and contiguous meningeal tissues was present (figs. 1 and 2). As for the vascular lesions, it was of particular interest that, just as in the case of human tuberculous meningitis, the bacilli showed a marked tendency to settle about the small meningeal blood vessels, and the accumulation of cells in and about the walls of these vessels was identical with that which, in the human being, as we have said, has been regarded as evidence of the infection of the meninges by way of the blood stream (figs. 2 and 4). Sections of the meninges of the animals killed at different intervals after infection showed that the lesions began about the vessel and extended from the adventitia inward; but once well developed, with the endothelium lifted up over accumula-

tions of inflammatory cells and the media and adventitia infiltrated as well, the vascular alterations were indistinguishable from those in human tuberculous meningitis. It became clear, therefore, that the character of the lesions of the blood vessels in human meningitis could not be regarded as proof that the bacilli responsible for the lesions reached the meninges by way of the blood stream. Indeed, as later observations taught us, this question could have been settled by recourse to human pathological material itself, for if one examines the meningeal lesions in those cases of human tuberculous meningitis which are definitely the result of the extension of infection from a local tuberculous focus in the complete absence of blood-stream infection (miliary tuberculosis), it will be seen at once that the typical vascular alterations are present in as great an abundance as they are in cases associated with miliary tuberculosis and blood-stream infection (fig. 3).

It is of considerable interest that ependymal "tubercles," similar to those which regularly roughen the lining of the ventricles in human cases, developed in our experimental animals in which the meninges on the convex surface of the brain were directly infected. Since the flow of cerebro-spinal fluid is from the ventricles outward and upward over the convex surface of the brain toward the sagittal sinus, it has been thought that the presence of tubercles on the surface of the ventricular linings indicates that the bacilli pass from the blood through the choroid plexus into the cerebro-spinal fluid and thence to the subarachnoid space, some stopping to infect the ventricles on their way. However, although a diffusion-like movement of cerebro-spinal fluid does undoubtedly occur in the direction stated above, this flow is hardly to be regarded as a forceful streaming of fluid which acts to prevent a retrograde passage of particulate matter. Carbon particles placed in the subarachnoid space about the spinal cord commonly travel upward and into the ventricles in spite of the movement of the cerebro-spinal fluid outward from the ventricles; and it was clear from our experiments that tubercle bacilli placed in the meninges upon the surface of the brain gradually found their way through the cerebro-spinal fluid backward into the ventricles. As a matter of fact, those experiments merely reproduced the state of affairs which can easily be observed in human autopsy material in the cases in which meningitis results from the extension of infection from a local tuberculous focus in the absence of blood-

stream infection; for in such cases, in spite of the fact that infection from the blood by way of the choroid plexus is precluded, the lining of the ventricles will regularly be found to be studded with tubercles as a result of the retrograde passage of bacilli. It may be remarked in this connection that these ependymal tubercles occur only in association with diffuse meningitis. No matter how severe a blood-stream infection there may be, with tubercles studding the thoracic and abdominal viscera, the ventricular lining will not be infected in the absence of meningitis. That extreme degrees of miliary tuberculosis occur without ventricular or meningeal infection is evidence that bacilli do not tend to pass readily from the blood through the choroid plexus into the cerebro-spinal fluid.

MORPHOLOGICAL STUDY OF HUMAN CASES

The above considerations combine to cast grave doubt on the immediate haematogenous origin of tuberculous meningitis, and forcibly direct attention to the more probable origin from local tuberculous foci, older than the meningitis, which infect the adjacent meninges by discharging bacilli directly into them. It is obvious that such foci might be situated (1) in the bones which enclose the central nervous system; (2) in the meninges themselves; and (3) in the substance of the brain. We therefore set about to search for such foci of origin in the cases of tuberculous meningitis available for study in this department. Most of our material at the beginning consisted of brains hardened in formalin and preserved for teaching purposes. Sometimes the entire spinal cord was available as well. The adjacent bones were only exceptionally preserved in the cases available in the store-rooms of our department.

Extension from Caseous Foci in Adjacent Bones. We have in our series only one case of tuberculous meningitis clearly arising from direct extension of infection from tuberculous vertebrae. In this case, the infection extended from the caseous vertebrae to the spinal cord, producing about the cord at that level a dense meningitis which diminished somewhat in intensity as it extended to the brain from the site of origin. Although this manner of origin is uncommon, it is of importance that the vertebrae as well as the middle ears (tuberculous otitis media and mastoiditis) be not neglected in a thorough search for

the origin of a given case of tuberculous meningitis. Crowe (15), particularly, has directed attention to the importance of tuberculosis of the middle ear as a source of tuberculous meningitis.

Extension from Caseous Foci in the Meninges Themselves. Our examination of the central nervous system consisted first in a careful scrutiny of the meninges in a search for tuberculous foci older than the meningitis. Such foci we have found not infrequently in the form of flattened, caseous plaques, partly or completely encapsulated, which are sharply enough outlined on the surface of the brain and which extend ordinarily into adjacent sulci. Sometimes they are entirely hidden in a sulcus, and are found only when the brain is sectioned. They vary in size from a few millimeters to more than a centimeter in diameter. They occupy the meningeal spaces and sometimes encroach slightly upon the adjacent cortex. These plaques are nothing more or less than solitary caseous tubercles of the meninges. They are entirely comparable to the more frequent solitary tubercles in the substance of the brain; and, like the latter, they are the result of the lodging of bacilli disseminated from some distant tuberculous lesion during any of the frequent periods of bacillaemia which are well known to occur during the progression of a tuberculous lesion anywhere in the body. They may be found well encapsulated and quiescent, in the absence of diffuse meningitis; or, spreading during a period of lowered resistance, they may discharge bacilli into the adjacent meninges and so become directly responsible for the development of diffuse meningitis. That such meningeal tubercles may give rise to meningitis has long been recognized, especial attention having been directed to them by Korteweg (16). While they are not at all rare, in our material the meningitis has been much more frequently occasioned by foci situated in the substance of the brain. The recent case of a woman dying during late pregnancy from tuberculous meningitis (autopsy 10249) illustrates very well the origin of meningitis from a caseous plaque. Aside from several calcified mesenteric lymph nodes the most careful search revealed no other visceral tuberculosis, and there was no miliary tuberculosis. An old caseous meningeal plaque was found in the Rolandic fissure on the right side, and that the much fresher meningitis resulted from extension from this meningeal tubercle was perfectly clear from the manner in which the inflammatory reaction radi-

ated from the plaque as a centre, the opposite side of the brain showing far less meningitis. This appears clearly to be a case in which the quiescent bacilli in a meningeal tubercle of long standing became reanimated during the decline of acquired resistance to tuberculosis which is well known to occur during pregnancy and the puerperium. Breaking through the wall of the tubercle they infected the surrounding meninges. Such an event is in all important respects comparable to the rapid extension of quiescent pulmonary lesions which not uncommonly takes place during pregnancy. Figs. 5, 6, 7 and 8 illustrate clearly the manner in which caseous meningeal plaques give rise to diffuse meningitis. From the table below it will be seen that such meningeal plaques were found to be the sole origin of a fresher diffuse meningitis in 17 of the 82 cases of meningitis in our series.

Extension from Caseous Foci in the Substance of the Brain or Spinal Cord. The occurrence of meningitis as a result of the extension of infection from the so-called solitary or conglomerate tubercles in the brain substance is a well recognized phenomenon, but cases of meningitis in which such an origin has been demonstrated have been decidedly exceptional in the literature and in general experience. Conversely, even when adjacent to the meninges large solitary tubercles of the brain often fail to give rise to meningitis. This is, perhaps, not to be wondered at, if we consider the factors which are concerned in the infection of the meninges by large tuberculomas. In the first place, such large foci may be the result of infection of the brain during the dissemination of bacilli throughout the body which practically always occurs to some degree during the primary infection before resistance has become well established. In such a case, if the focus extends rapidly and progressively but remains situated deep in the brain substance, it has no opportunity to infect the meninges; whereas if it begins at a site near the meninges, it will produce fatal meningitis by direct extension before it has had an opportunity to attain any great size. On the other hand, the infection of the brain substance may result from one of the periods of bacillaemia which are well known to occur during any progressive, visceral lesion which occurs after resistance has once been acquired. In such a case, the tuberculoma will develop under the influence of some degree of resistance and, just as in the case of adult chronic phthisis, its progress will be retarded and the opportunity for connective-

tissue formation (encapsulation) increased. Large tuberculomas of the brain are, therefore, usually encapsulated, and even when they reach the meninges the bacilli in their margins are not very numerous, and ordinarily only a local and low grade meningitis with subsequent fibrosis occurs. For a tuberculous focus to set up a diffuse meningitis bacilli must be discharged freely from the margin and it is only a softened caseous margin containing many bacilli which is effective in establishing a diffuse and progressive meningitis. It is clear, then, that only under two circumstances can large tuberculomas serve as the source of meningitis; first, a focus beginning deep within the brain during the primary infection can progress rapidly to reach such a size that it comes into contact with the ventricles or the meninges. This does occur but it is not usual for tuberculomas, whether in the brain or in other solid viscera, to attain a great size before some degree of resistance appears which slows their growth and so provides opportunity for encapsulation as the mass extends. In the second place, arising either during the bacillaemia of the primary or subsequent infection, but arrested by the effect of acquired resistance, an encapsulated tuberculoma in contact with the meninges or ventricles may become reanimated during a period of depressed resistance; the bacilli begin to proliferate, the encapsulating connective tissue is destroyed and infection of the meninges occurs. This, too, is rather uncommon for it is uncommon for resistance, once having been established, to fall to such a low level (and remain there) that unrestricted proliferation of bacilli can take place. But it does occur, and we have such cases in our series, one of which we have described above. However, we realized at the outset in our search for intracerebral foci of origin in the cases of meningitis at our disposal, that if such foci were actually present they would not commonly be the larger masses several centimeters in diameter, which everyone knows are ordinarily well encapsulated, but that they would be smaller, freshly caseous foci, containing many bacilli, which arose near the meninges or ventricles and had not existed long enough to be well encapsulated. In order properly to search for such foci it was necessary to cut the brains in slices so thin that no single slice would be thick enough to hold in its substance a small caseous mass in communication with the meninges or the ventricles. Such a procedure is most tedious and time-consuming, but we have

learned to realize that unless the entire brain and spinal cord are cut in slices not thicker than three millimetres the chances are quite against finding such foci as may be present, even when they have a diameter somewhat greater than three millimeters. By sparing no pains in the search, however, we have found caseous tubercles, usually multiple, embedded in the cortex and discharging into the adjacent meninges in most of the cases of tuberculous meningitis which we have examined, as Table I will show. Figs. 9 through 17 illustrate the gross appearance of such tubercles. These small caseous tubercles, from three to five millimeters in diameter, are often most surprisingly difficult to see on the cut surface of a brain hardened in formalin. Indeed, more than once on re-examination of a brain said to be free from tubercles it has been our experience to find caseous foci as large as five millimeters in diameter exposed, unnoticed, on the cut surfaces of brains sectioned in this department in which particular attention is devoted to the search for these foci. We have in our material many caseous tubercles exposed in cross section which ordinarily have to be pointed out before they are recognized by observers examining the slices of the brain for the first time. Some of these tubercles were discovered by ourselves only by reason of the difference in density of the area when examined by transillumination. Not all caseous tubercles, of course, are so difficult to see on the cut surface. Many stand out in sharp contrast to the gray or white matter. But in the hardened brain they are often so nearly the color of the brain substance that it may be quite impossible to obtain a revealing photograph, regardless of what filters one chooses to use. We stress this difficulty of exposing and of seeing these foci because we wish to emphasize the importance of reducing the central nervous system to thin, translucent slivers and of examining the cut surfaces minutely if one wishes to find these caseous masses which we have every reason to regard as sites of origin of most cases of tuberculous meningitis. We have found a light, flat knife with a blade about a foot long and an inch in width to be best suited for thin slicing of the brain. A heavy knife, or one with a decidedly wedge-shaped blade, is unsatisfactory for the purpose. Slicing by hand, although more laborious, has been a more sure method of search than the use of a guillotine. One is quite frequently guided to the sites of the discharging caseous foci by the fact that the meninges on the

TABLE I

AUTOPSY NUMBER	AGE	MENINGITIS	MILIARY TUBERCULOSIS	DEMONSTRATED EXTENSION OF INFECTION FROM OLDER LESION IN				OLDER FOCI IN BRAIN OR CORD NOT DISCHARGING BACILLI	ENCAPSULATED QUIESCENT FOCI IN MENINGES
				Brain	Meninges	Bones	Choroid plexus		
6620	18 mos.	+	+	+	0	0	0	+	0
7410	14 mos.	+	+	+	0	0	0	−	−
7465	5 mos.	+	+	+	0	0	0	+	0
7477	3½ yrs.	+	+	+	0	0	0	−	−
7498	2 yrs.	+	+	+	0	0	0	−	−
8080	9 yrs.	+	+	+	0	0	0	+	0
8139	3 yrs.	+	+	+	0	0	0	+	0
8191	11 mos.	+	+	+	0	0	0	+	0
9048	3 yrs.	+	+	+	0	+*	0	−	−
9281	14 mos.	+	+	+	0	0	0	+	0
9473	2 yrs.	+	+	+	0	0	0	+	0
9575	1 yr.	+	+	+	0	0	0	+	0
9667	7 yrs.	+	+	+	0	0	0	+	+
9677	7 yrs.	+	+	+	0	0	0	+	0
9690	8 mos.	+	+	+	0	0	0	+	0
9803	2 yrs.	+	+	+	0	0	0	−	−
9915	2 yrs.	+	+	+	0	0	0	+	0
10185	4½ yrs.	+	+	+	0	0	0	+	0
10299	3 yrs.	+	+	+	0	0	0	+	0
10354	3 yrs.	+	+	+	0	0	0	+	+
12584	17 mos.	+	+	+	0	0	0	−	−
10478	18 mos.	+	+	+	0	0	0	+	+
10517	2½ yrs.	+	+	+	0	0	0	+	0
10606	12 yrs.	+	+	+	0	0	0	−	−
10705	45 yrs.	+	+	+	0	0	0	+	0
10809	4 yrs.	+	+	+	0	0	0	+	0
10851	1 yr.	+	+	+	0	0	0	+	0
10908	4 yrs.	+	+	+	0	0	0	+	0
10944	9 mos.	+	+	+	0	0	0	+	0
10965	8 mos.	+	+	+	0	0	0	+	0
10987	4 yrs.	+	+	+	0	0	0	−	−
11004	14 mos.	+	+	+	0	0	0	+	0
11202	2 yrs.	+	+	+	0	0	0	+	+
11219	11 yrs.	+	+	+	0	0	0	+	+
11541	9 yrs.	+	+	+	0	0	0	+	0
11548	16 yrs.	+	+	+	0	0	0	+	+
11943	21 mos.	+	+	+	0	0	0	+	+
12162	3 yrs.	+	+	+	0	0	0	+	0
12173	22 mos.	+	+	+	0	0	0	+	0
12297	3½ yrs.	+	+	+	0	0	0	0	0
12425	6 yrs.	+	+	+	0	0	0	+	0

TABLE I—*Continued*

AUTOPSY NUMBER	AGE	MENINGITIS	MILIARY TUBERCULOSIS	DEMONSTRATED EXTENSION OF INFECTION FROM OLDER LESION IN				OLDER FOCI IN BRAIN OR CORD NOT DISCHARGING BACILLI	ENCAPSULATED QUIESCENT FOCI IN MENINGES
				Brain	Meninges	Bones	Choroid plexus		
2518M	7 mos.	+	+	+	0	0	0	+	0
3171M	17 mos.	+	+	+	0	0	0	+	0
3248M	2 yrs.	+	+	+	0	0	0	+	0
3256M	27 yrs.	+	+	+	0	0	0	+	0
12402	17 mos.	+	+	+	+	0	0	−	−
8676	14 mos.	+	+	0	+	0	0	+	0
8681	2½ yrs.	+	+	0	+	0	0	0	0
9154	7 yrs.	+	+	0	+	0	0	+	0
10347	16 mos.	+	+	0	+	0	0	+	0
10812	4 mos.	+	+	0	+	0†	0	−	−
10907	5 mos.	+	+	0	+	0	0	+	0
11174	6 mos.	+	+	0	+	0	0	−	−
10388	3 yrs.	+	+	0	+	0	0	+	0
11239	2 yrs.	+	+	0	+	0	0	−	−
11353	3 yrs.	+	+	0	+	0†	0	+	0
11458	5 yrs.	+	+	0	+	0	0	+	+
11816	11 mos.	+	+	0	+	0	0	0	+
12184	12 mos.	+	+	0	+	0	0	0	0
3336M	9 mos.	+	+	0	+	0	0	+	0
8708	20 mos.	+	+	0	0	0	+	+	0
1766	35 yrs.	+	0	+	0	0	0	−	−
7508	3½ yrs.	+	0	+	0	0	0	0	0
8089	10 mos.	+	0	+	0	0	0	+	0
8300	18 yrs.	+	0	+	0	0	0	+	0
8633	56 yrs.	+	0	+	+	0	0	+	+
10191	15 mos.	+	0	+	0	0	0	+	0
10920	18 mos.	+	0	+	0	0	0	−	−
11940	2 yrs.	+	0	+	0	0	0	+	0
11335	2 yrs.	+	0	+	0	0	0	+	0
1467M	36 yrs.	+	0	+	0	0	0	+	0
7075	6 mos.	+	?§	+	0	0	0	−	−
482M	9 mos.	+	0	0	+	0	0	0	0
10249	17 yrs.	+	0	0	+	0	0	0	0
12150	30 yrs.	+	0	0	+	0	0	+	0
12401	6 yrs.	+	0	0	+	0	0	0	0
8634	24 yrs.	+	0	0	0	+‡	0	0	0
8201	2 yrs.	+	0	0	0	0	0	−	−
11249	6 yrs.	+	0	0	0	0	0	+	0
8044	2½ yrs.	+	+	0	0	0	0	+	0
9732	10 yrs.	+	+	0	0	0	0	+	0
11151	6 wks.	+	+	0	0	0	0	+	0

TABLE I—*Concluded*

AUTOPSY NUMBER	AGE	MENINGITIS	MILIARY TUBERCULOSIS	DEMONSTRATED EXTENSION OF INFECTION FROM OLDER LESION IN				OLDER FOCI IN BRAIN OR CORD NOT DISCHARGING BACILLI	ENCAPSULATED QUIESCENT FOCI IN MENINGES
				Brain	Meninges	Bones	Choroid plexus		
7722	24 yrs.	0	+	0	0	0	0	+	0
7743	11 mos.	0	+	0	0	0	0	+	+
7750	3½ yrs.	0	+	0	0	0	0	+	0
7948	8 mos.	0	+	0	0	0	0	+	0
10322	37 yrs.	0	+	0	0	0	0	+	0
10382	4 mos.	0	+	0	0	0	0	+	0
10477	20 mos.	0	+	0	0	0	0	+	0
10831	8 wks.	0	+	0	0	0	0	+	0
10895	58 yrs.	0	+	0	0	0	0	−	−
11164	28 yrs.	0	+	0	0	0	0	+	+
12415	26 yrs.	0	+	0	0	0	0	0	0

− indicates that the brain was not completely sectioned in a search for foci.

* Caseous tuberculous otitis media and mastoiditis with extension of infection into jugular fossa.

† Caseous tuberculous otitis media and mastoiditis without extension to meninges.

‡ Extension of infection from caseous vertebrae.

§ Autopsy restricted to examination of brain.

TABLE II

Analysis of table I

	NUMBER OF CASES
Total cases studied	93
Tuberculous meningitis	82
Miliary tuberculosis	75
Meningitis with miliary tuberculosis	64
Meningitis without miliary tuberculosis	17
Miliary tuberculosis without meningitis	11
Origin of meningitis from older focus in brain	56
Origin of meningitis from older focus in meninges	17
Origin of meningitis from older foci in both brain and meninges	2
Origin of meningitis from older focus in vertebrae	1
Origin of meningitis from older focus in choroid plexus	1
Origin of meningitis not found	5
Caseous foci found in brain not discharging into meninges	66
Encapsulated quiescent foci in meninges	13

surface of the brain often show distinctly more exudate over those regions. In our material the caseous foci have been most frequently situated in the temporal and parietal lobes and in the cerebellum, less often in the frontal and occipital lobes. It is of interest that, regardless of where the discharging focus may be, when meningitis is *well established*, the familiar accumulation of exudate at the base of the brain is always present. The basal exudate will be regularly found in cases in which, for example, the meninges are infected from a caseous focus situated on the convex surface of one hemisphere, in the complete absence of blood-stream infection (miliary tuberculosis). In occasional cases, however, death occurs before the spread of a frank, macroscopic meningitis has progressed very far from the site of origin, and in these cases only a minimal and microscopic amount of exudate is found at the base.

Cases of Miliary Tuberculosis without Meningitis. Table I contains eleven examples of miliary tuberculosis without tuberculous meningitis. These cases (to which numerous others in our records could have been added) include those of individuals ranging in age from eight weeks to fifty-eight years. They have been selected as instances of particularly heavy infection of the blood stream and of all of the tissues of the body which are regularly involved in miliary tuberculosis. It will be seen in the table that in all except two of these cases tuberculous areas were discovered in the substance of the central nervous system but not in communication with the meninges, and that in two of the cases encapsulated tuberculous foci were found in the meninges themselves. The extension of any of these foci to feed their contained bacilli into the subarachnoid space would have led to the appearance of meningitis. In autopsy no. 11164 the miliary tuberculosis was produced by the discharge of many bacilli into each of several large pulmonary veins from adjacent caseous foci—a circumstance which, when it occurs, always leads to the most extreme miliary tuberculosis. However, in spite of the fact that the liver, spleen, bone-marrow, lungs and kidneys were riddled with tubercles, and in spite of the fact that the discharge of bacilli into the pulmonary veins leads to their direct transport in abundance from the left ventricle to the meninges, meningitis did not occur; and this case is typical of them all. On careful search however, minute, rare, discrete miliary tubercles were

found in the brain and meninges in each case, and the character of these tubercles was always that of the miliary tubercles elsewhere in the body (Figs. 19, 20, 21, 22). It is of particular interest that diffuse meningitis did not occur even in the cases in which the viscera were riddled with the type of rapidly caseating miliary tubercles which we have described elsewhere as "soft" tubercles, since they appear as foci of necrosis rather than as compact epithelioid-cell tubercles, and which we have shown to be the result of a heavy blood-stream infection in an individual with a high degree of allergy (13). If miliary tuberculosis were able under any circumstances to produce meningitis by direct and immediate haematogenous infection of the meninges, such cases as these should provide the most ideal conditions imaginable; but instead, these cases show only rare, discrete soft tubercles here and there in the meninges (Figs. 21 and 22).

It is such cases as these, which must be familiar to every pathologist who gives attention to the matter, that make it evident that a heavy blood-stream infection is, in itself, not sufficient to produce tuberculous meningitis—not even in a highly allergic individual. Bacilli do not stop in the meninges in sufficient numbers. Such human cases are the analogues of the experimental intravascular injections of tubercle bacilli which we have described above, and which, in neither our own nor in others' experience, lead to the direct production of meningitis. It is, however, obvious that if the bacilli in any of the sparsely scattered miliary tubercles of the brain or meninges continue to proliferate, larger caseous foci may develop which later may feed their bacilli into the subarachnoid space and so establish a diffuse meningitis. The "soft" miliary tubercle would be best fitted for this, for it contains from the beginning more bacilli than the ordinary compact tubercle (13). But the development of diffuse meningitis is contingent upon the fortuitous development of discharging, caseous foci and not upon the mere presence of large numbers of bacilli in the blood stream (miliary tuberculosis).

DISCUSSION

As Table I will show, we have examined 82 cases of tuberculous meningitis in the search for local, older tuberculous foci communicating with the meninges or ventricles, and we have found such foci, whether

in the adjacent bones, in the substance of the brain or spinal cord or in meninges themselves, in 77 of those cases. In each of the 5 cases in which we failed to find discharging foci, the material available for study was incomplete. In 4 of these 5 cases old caseous foci were found in the brain substance, and in 2 of them the meningitis occurred in the absence of miliary tuberculosis, excluding even the possibility of direct haematogenous infection. We feel that the theoretical morphological and experimental considerations outlined above, coupled with the frequency with which we have found caseous foci discharging into the meninges, justifies the view that the origin of tuberculous meningitis is to be referred to the infection of the cerebrospinal fluid from these local tuberculous foci by means of direct extension rather than to the immediate haematogenous infection of the meninges which has been so widely postulated.

The older caseous foci which we have found discharging into the meninges or ventricles have been situated, most commonly, in the substance of the brain; next in frequency are those in the meninges; foci in the bones, or in the spinal cord, responsible for the occurrence of meningitis, are much less common. We have carefully studied the choroid plexus, and while it is true that infection of some part of the plexus is the rule in most cases of advanced tuberculous meningitis, we have only one case in which the plexus could be incriminated as the site of origin of the meningeal infection. In this case an old caseous mass situated in the choroid plexus discharged its bacilli into the ventricle. Similar caseous foci were found in the brain substance but none in communication with the meninges or ventricles. In the rest of our cases the infection of the plexus appeared to be of the same age and was of the same character as the meningitis, or else was distinctly fresher. Ordinarily the only lesions found in the plexus were minute microscopic ones. After the preliminary account of our work on tuberculous meningitis was published (13) we were able to secure through the courtesy of Dr. Esmond R. Long, a copy of a paper by Kment (2) which was not available in the Surgeon General's Library. In this paper, Kment questioned the haematogeneous origin of tuberculous meningitis, and suggested that haematogeneous lesions in the choroid plexus are most frequently responsible for the meningeal infection. We cannot subscribe to that view, for aside from the fact

that we have found macroscopic caseous lesions elsewhere which account for the meningitis without forcing the microscopic infection of the choroid plexus into the question, the character of the plexus lesions in all of our cases except the one mentioned, and indeed in almost all of Kment's cases, renders them insignificant as sources of origin of the heavy meningeal infection.

Kment seems not to have considered the possibility that the choroid plexus can be infected secondarily from the meningitis, just as is the the lining of the ventricles, and yet this is a very regular occurrence. Fig. 18 shows infection of the choroid plexus of the type described by Kment as arising from blood stream infection and leading to meningitis, but in this instance (and we could show the same for our other cases) the infection was clearly secondary to the meningitis. This was in an adult (autopsy 8633) who died of tuberculous meningitis in the complete absence of miliary tuberculosis. There was an extensive meningitis, prominent about several older caseous masses in the cortex and meninges which were discharging bacilli into the cerebrospinal fluid but, as usual, the exudate was abundant and fresher at the base. There was the usual granular tuberculous ependymitis, and the choroid plexus showed the amount of infection ordinarily seen in tuberculous meningitis. Our cases of meningitis without miliary tuberculosis show clearly that the involvement of the plexus can result from direct infection from the cerebrospinal fluid in the absence of blood-stream infection.

What is the origin of the local caseous foci which give rise to meningitis? Some are undoubtedly the result of the early dissemination of bacilli which so commonly takes place during the primary infection. Others result from dissemination occurring as a result of reinfection. No matter what the site of a progressing lesion in man or in the experimental animal may be, a scattering of bacilli to distant organs by way of the blood stream is exceedingly common, and the results of this dissemination are, ordinarily, the sparsely scattered tuberculous masses ("solitary tubercles") of varying size, with or without competent encapsulation, which are so frequently found in distant organs at autopsy. Many of these foci become sterile. In others bacilli remain alive, but, in the presence of acquired resistance, their power of multiplication is held in abeyance and the focus may remain quiescent for

years, to suffer, perhaps, a recrudescence of activity either because of obscure, favorable local conditions, or as a result of a general depression of acquired resistance, as in the case of the woman discussed above who developed meningitis during the puerperium. In the case of the early dissemination which so commonly occurs during the primary infection before there has been time for the development of acquired resistance, the scattered foci may enlarge progressively without any significant encapsulation, and this, undoubtedly, is the situation represented by most of the caseous foci which extend to infect the meninges in infancy and early childhood. It is, of course, not in the central nervous system alone that such foci become reanimated and dangerous; the same event occurring in the kidney, the prostate, the Fallopian tube, the bones and elsewhere, leads to tuberculous alterations of these sites familiar to every pathologist.

In infancy, and in early childhood, miliary tuberculosis is so commonly associated with tuberculous meningitis that the latter has long been assumed to be simply a manifestation of the former. This is a type of *cum hoc ergo propter hoc* reasoning, against which, in the present instance, there are numerous and weighty objections. We have already called attention to such objections as (1) cases of miliary tuberculosis of extreme degree without meningitis; (2) cases of meningitis without miliary tuberculosis; and (3) lack of correlation between the age and character of the meningitis and of the miliary tubercles in other viscera in many cases in which meningitis and miliary tuberculosis do exist together. How then explain the unquestioned frequency of the coincidence of meningitis with miliary tuberculosis in children (for the association is far less common in adults)? We believe that one should stress not so much the coincidence of meningitis with miliary tuberculosis, as the coincidence of meningitis with a low degree of acquired resistance. If one examines the protocols of cases of tuberculous meningitis in infancy and early childhood, there will almost always be found a record of extensive, progressive pulmonary, lymph node, intestinal or other visceral tuberculosis. Now such progressive lesions in the first months or years of life ordinarily represent the results of infections which were too heavy to be held in check satisfactorily until acquired resistance could develop to a degree sufficient to inhibit the progress of the disease. They are comparable to the re-

sults of a fairly heavy primary experimental inoculation; and, as is well known, a rather rapid and progressive haematogenous dissemination of bacilli occurs under such circumstances, with the result that wherever the disseminated bacilli lodge they come to rest in tissues without any very appreciable degree of acquired resistance, and the bacilli can proliferate there and lead to the formation of tubercles of varying size. It is to be expected, therefore, that in cases of progressive primary infection in early life there will be a greater opportunity for the development of macroscopic caseous tubercles in the central nervous system than there will be in cases of reinfection in adult life, in which bacilli disseminated from the progressive lesions fall upon unfavorable soil because of the presence of resistance acquired during an earlier, primary infection. For the same reasons it is much more common to find macroscopic, caseous tubercles in the spleen, for example, in association with pulmonary tuberculosis in childhood than in association with adult chronic phthisis, although it is a well known fact that tubercle bacilli are scattered over the body by way of the blood stream in the latter condition as is demonstrated by the occurrence of repeated periods of bacillaemia provable by blood culture. As for the more frequent occurrence of miliary tuberculosis in early life, that is the expected result of progressive primary lesions in contrast to the progressive lesions of reinfection in the body with acquired resistance for reasons which we have discussed at length in another place (13). In brief, the sequence of events is not (1) primary lesion, (2) meningitis occurring as a part of a miliary tuberculosis; but rather (1) primary lesion, (2) dissemination of bacilli leading to formation of caseous foci in viscera and in structures adjacent to meninges, with or without frank miliary tuberculosis, (3) discharge of bacilli from these foci into the meninges causing meningitis. Isolated tubercles of the brain or meninges arising as part of a slowly progressing miliary tuberculosis may at times develop into caseous foci large enough to infect the cerebrospinal fluid by discharging large numbers of bacilli directly into it. The development of meningitis, however, is a fortuitous event, depending not upon the existence of miliary tuberculosis but upon the chance extension of infection from an established, caseous focus which happened to develop adjacent to the meninges or ventricles.

SUMMARY

Experimental and morphological evidence is presented which demonstrates that diffuse tuberculous meningitis is not a direct and immediate result of haematogenous infection of the meninges. Miliary tuberculosis produces only rare, sparsely scattered tubercles in the meninges, not diffuse meningitis. Tuberculous meningitis has its origin in the discharge of bacilli into the cerebrospinal fluid from adjacent, older caseous tuberculous foci. Such discharging foci have been found, by careful search, in the substance of the brain or cord, in the meninges, in the bones encasing the central nervous system, or in the choroid plexus in 77 of the 82 cases of meningitis in our series. In all except 2 of these 77 cases the demonstrated source of the diffuse meningitis was situated in the substance of the central nervous system or in the meninges. In the 5 cases in which no local focus was found the material for study was incomplete.

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EXPLANATION OF FIGURES

FIGS. 1 AND 2. Tuberculous meningitis produced by injecting virulent bovine bacilli into the subarachnoid space of an allergic rabbit. The lesion is characteristic of that in human tuberculous meningitis—inflammatory outpouring of fluid and a predominantly mononuclear-cell exudate with caseation of the exudate and meningeal tissues. Fig. 2 shows early involvement of a meningeal artery.

(Photographs by Mr. Milton Kougl)

FIGS. 3 AND 4. Characteristic vascular involvement with prominent intimal infiltration which has been widely regarded as evidence that the infection of the meninges enters from the blood stream directly through the small meningeal vessels during miliary tuberculosis. However, Fig. 3 is from a patient in whom meningeal infection arose from a cerebral tubercle in complete absence of miliary tuberculosis; and Fig. 4 is from a rabbit in which the meninges were directly infected. These cases show that the characteristic vascular involvement is no proof that the vessels were infected from within.

FIG. 5. Meningitis arising from caseous meningeal plaque (the white area) on the surface of the right hemisphere. The clouding of the meninges on that side is clearly seen in contrast to the clear meninges on the opposite side (human brain).

FIG. 6. Another meningeal plaque deep in a sulcus. This a is large plaque and it encroaches somewhat upon the brain substance but clearly arose in the meninges. Meningitis in this case was directly traceable to this source (human brain).

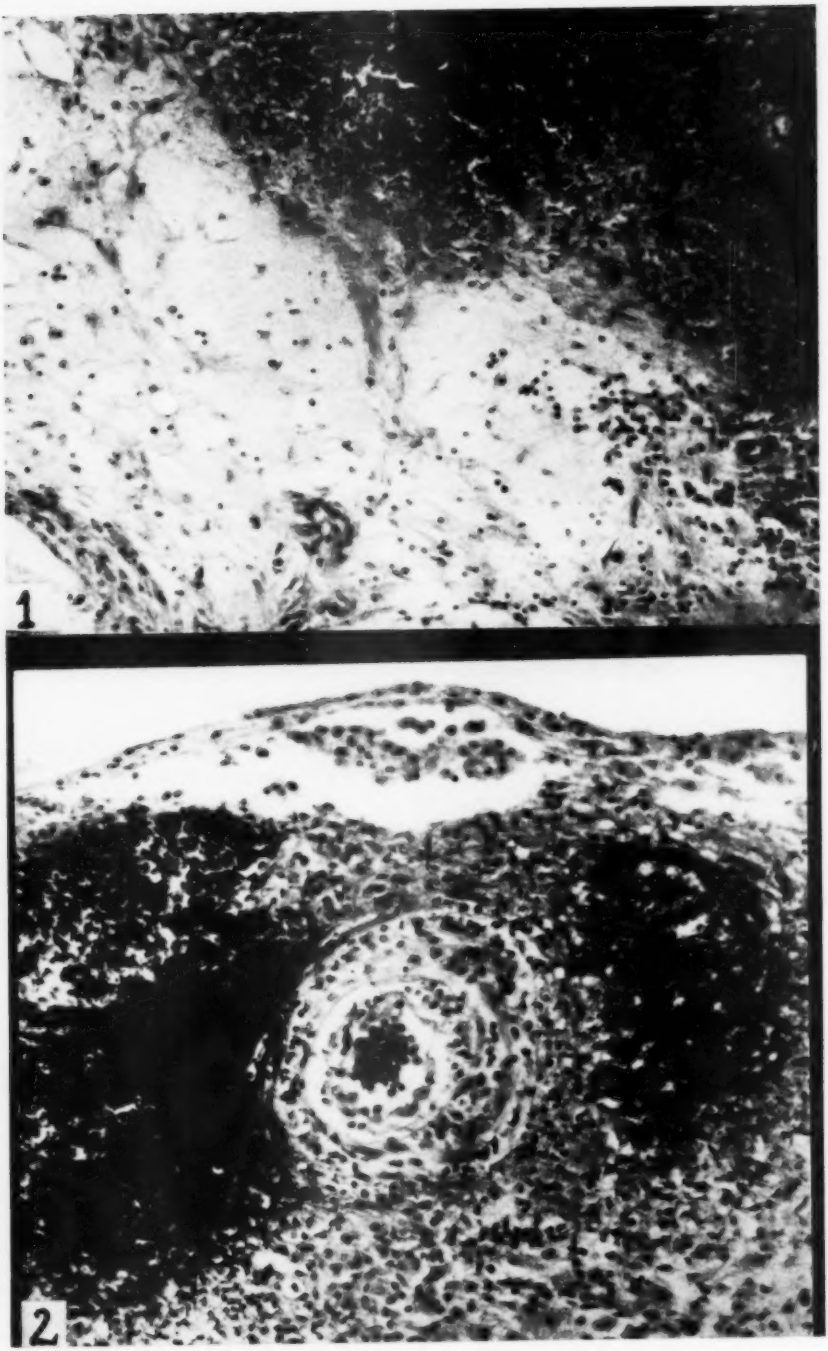
FIGS. 7 AND 8. Low power microphotograph of a meningeal plaque in another human case. This shows beautifully the manner of origin of meningitis from such foci. It can be seen that the caseous mass lies in a sulcus. The meninges are only beginning to be infected from this focus which is, on the surface of the brain, extending with caseous margin to discharge bacilli into the subarachnoid space. Fig. 8 is a higher power microphotograph to show the extending margin.

FIGS. 9 THROUGH 17. Characteristic caseous foci in the cortex from different human cases, extending to and infecting the cerebrospinal fluid with a resulting meningitis. Fig. 9 shown discharge of a caseous tubercle into a lateral ventricle. Fig. 13 shows small caseous mass adjacent to meninges and extending into them in a further section. There were numerous foci of this sort in this brain.

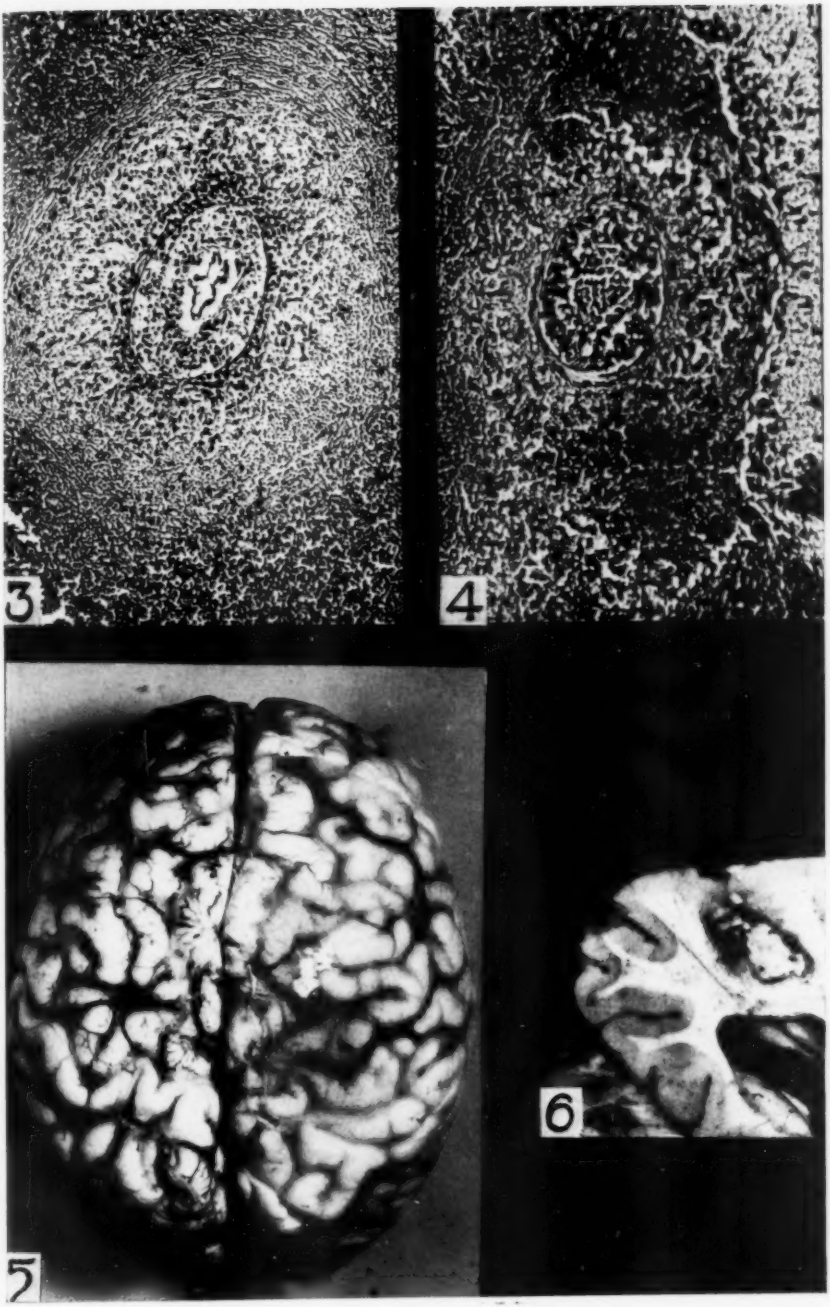
FIG. 18. Numerous caseous tubercles in choroid plexus in a human case in which meningitis resulted from extension from a cerebral caseous focus in complete absence of miliary tuberculosis. This shows that involvement of the choroid plexus is not dependent upon infection by way of the blood, but may be a result of the meningitis.

FIGS. 19 AND 20. Showing that diffuse meningitis is not merely a part of miliary tuberculosis. The lungs (Fig. 20) and other viscera were riddled with compact tubercles in this case, but the meninges were normal except for very rare, sharply localized miliary tubercles of the same character as those in viscera (human case).

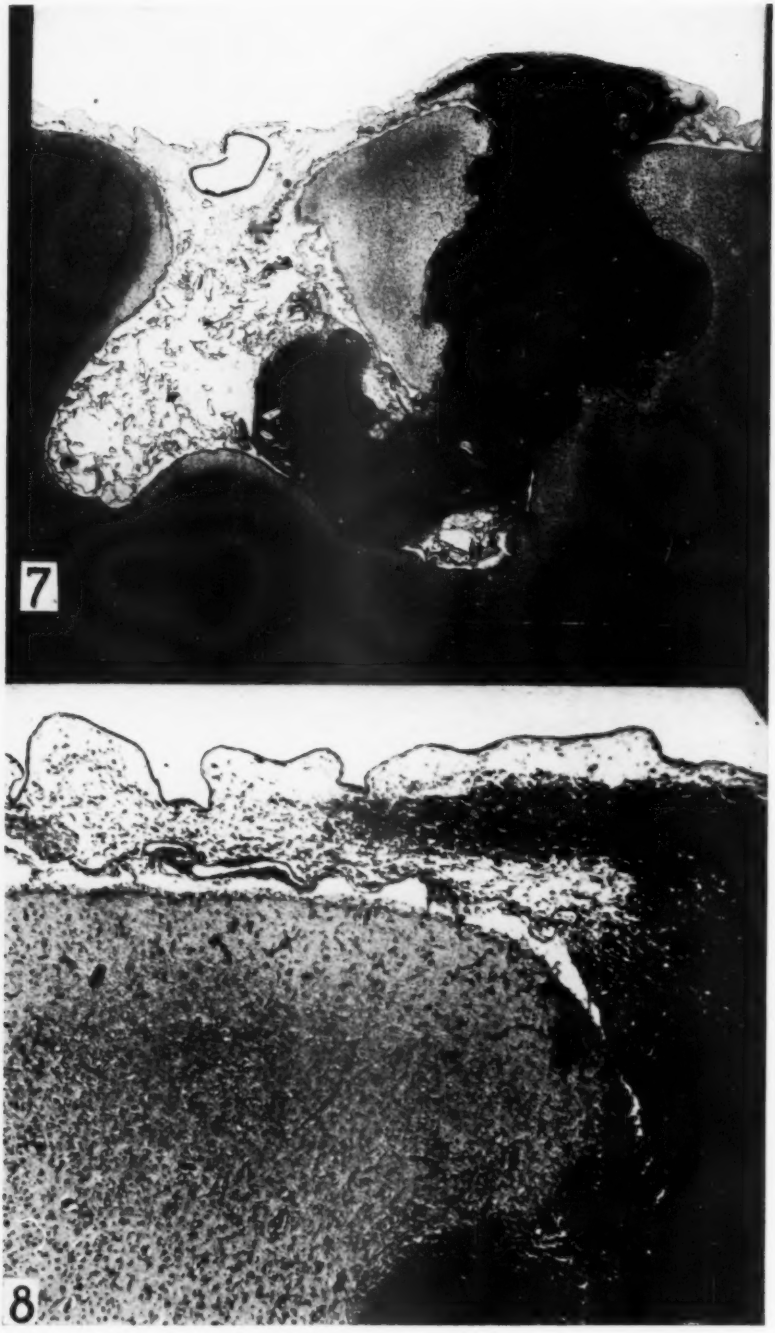
FIGS. 21 AND 22. Showing that heavy blood stream infection produced by discharge of great numbers of bacilli into pulmonary vein in an allergic person produces only rare miliary tubercles of the meninges, not diffuse meningitis. The liver (Fig. 21) and other viscera were peppered with caseous miliary tubercles of the "soft" variety which appear as foci of necrosis, each swarming with bacilli; in the meninges only very rare, sharply localized tubercles of the same size and nature, but no diffuse meningitis.



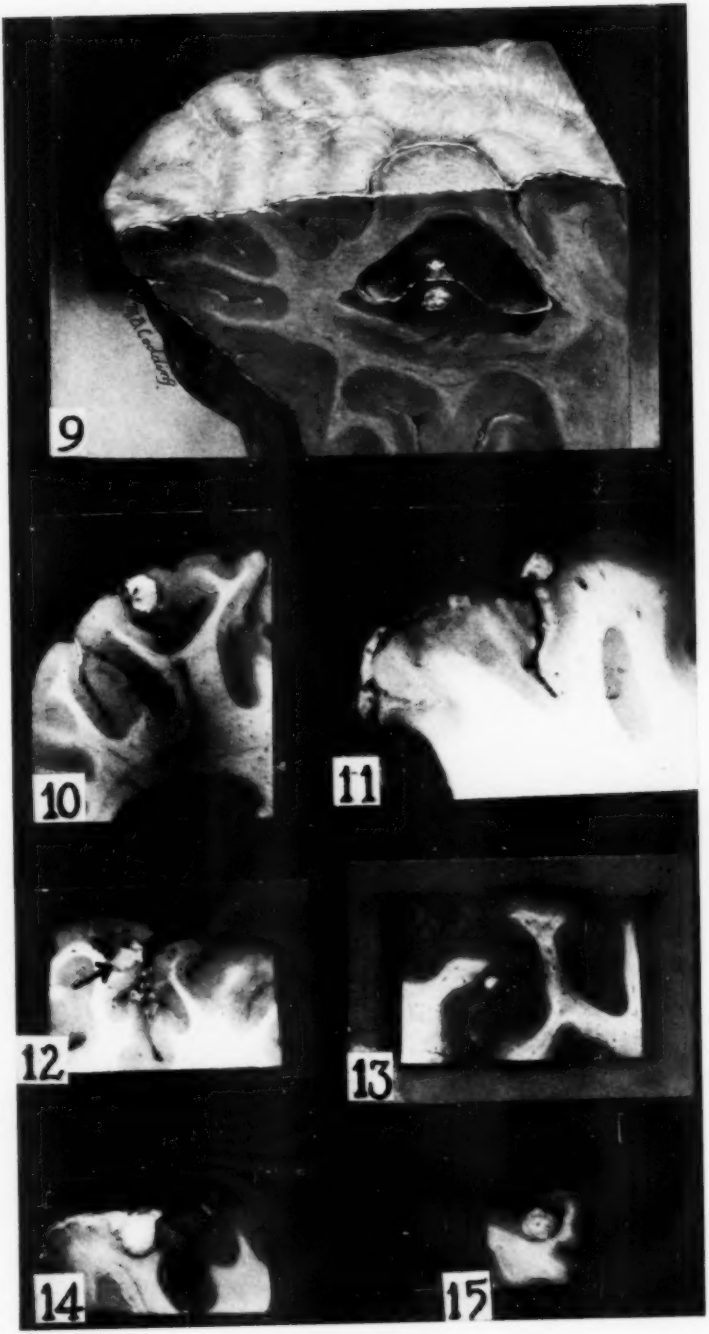
FIGS. 1 AND 2



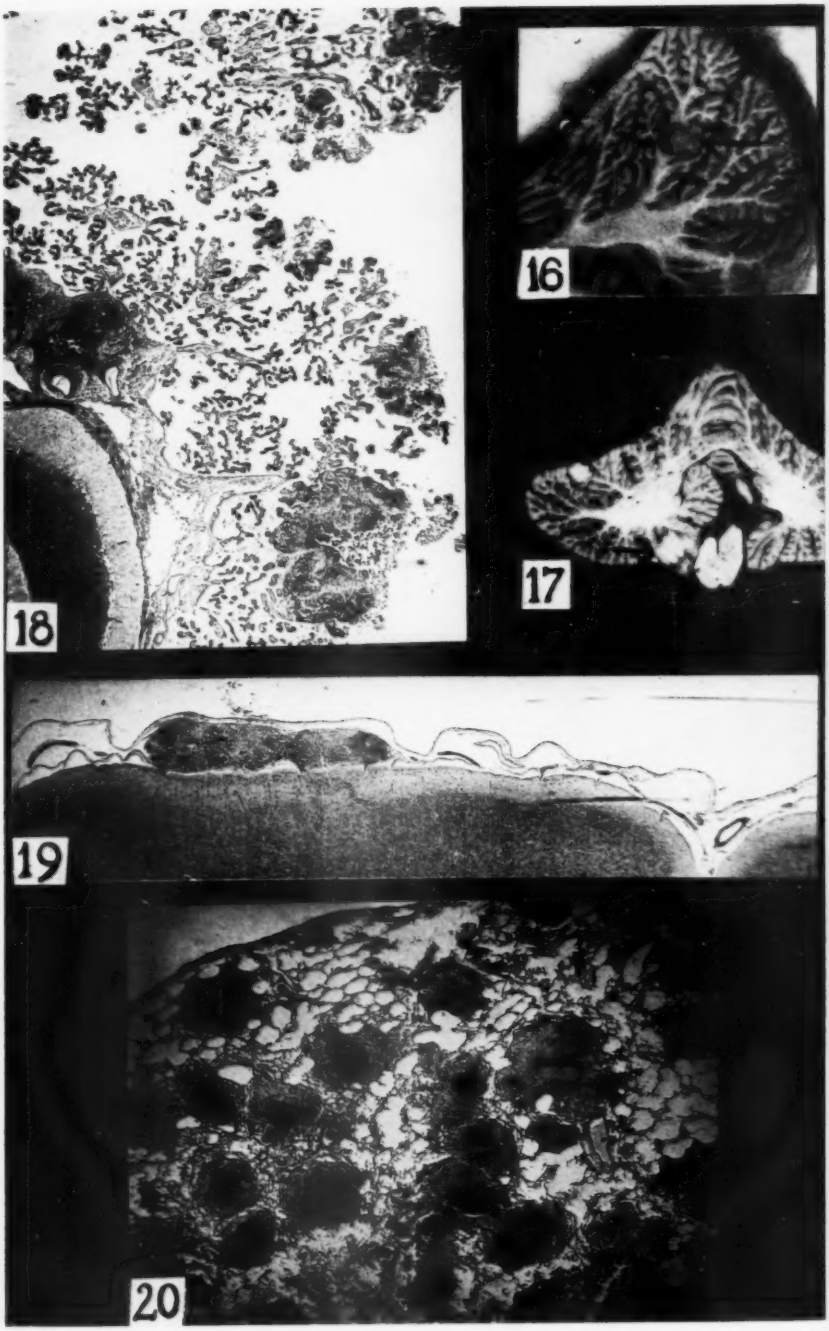
FIGS. 3–6



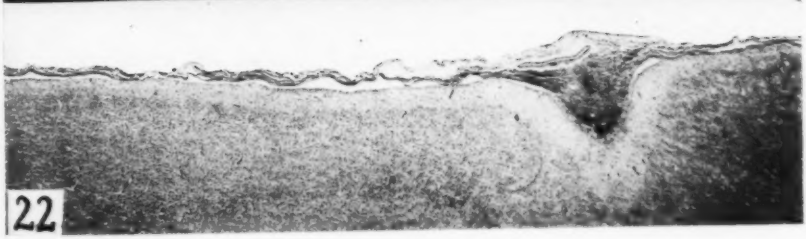
FIGS. 7 AND 8



FIGS. 9–15



FIGS. 16–20



FIGS. 21 AND 22

JAKE PARALYSIS[1]

Paralysis Following the Ingestion of Jamaica Ginger Extract Adulterated with Tri-ortho-cresyl Phosphate

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I. INTRODUCTION

Early in the year 1930 many persons throughout the South suddenly became afflicted with a peculiar type of paralysis which manifested itself chiefly as bilateral foot-drop and wrist-drop. It is impossible to ascertain just where the first cases were seen but almost simultaneously the paralysis appeared in people in widely scattered communities and within a few months there were a large number in almost every State in the South. Outbreaks were also reported in Massachusetts and later in Southern California. The total number has not been definitely tabulated but reports (16) indicate that there were 4837 recorded by the end of the summer of 1930 and the director of the Bureau of Prohibition is said to have estimated that there were about 20,000.

It was soon recognized that this peculiar outbreak of paralysis was due in every instance to the antecedent ingestion of "Jake," an alcoholic beverage which is sold at many drug stores and confectionaries under the label "Fluid-extract of Jamaica Ginger U. S. P.," and that the symptoms were produced by some toxic agent or adulterant recently introduced into the manufacture of "Jake."

The present paper gives a summary of the literature that has ac-

[1] Various names such as Tri-o-cresyl Phosphate Poisoning, Jake Paralysis, Jake Neuritis, Jamaica Ginger Polyneuritis and Ginger Paralysis have been given to this disease. While Tri-o-cresyl Phosphate Poisoning is technically the most accurate and descriptive term, the slang designation "Jake" Paralysis conveys most appropriately the idea of an affection caused by drinking adulterated Jamaica Ginger Extract.

cumulated upon this subject and also reports experimental and pathological studies made by the authors.

II. HISTORICAL

Although this outbreak of paralysis is unique in so far as the etiology and clinical findings are concerned, several related points are of great historical interest.

The oleoresin of ginger was introduced into the U. S. Pharmacopoeia in 1863 and its various preparations are venerable domestic remedies for many ailments. Many therapeutically-inclined physicians have prescribed the drug for intestinal disturbances as a carminative and stomachic and it is used also to alleviate menstrual pain. For many years it has been taken by the laity as a panacea for any stomach trouble.

In addition to the legitimate use of ginger products, various adulterated alcoholic compounds have apparently been used as intoxicants for many years. Woods (2) quotes the Baltimore Sun of November 16, 1898: "There were two deaths in Oxford last week caused by drinking Jamaica Ginger used as a substitute for whiskey in dry places. The first to die was one Terry, a peripatetic individual, who spent most of his time in Oxford It is said he has a wife and children, but their residence is unknown. John Cousins, a permanent resident of Oxford, was the other victim of this pernicious habit." Thompson (1), Woods (2), and Stieren (3) reported a total of eight cases of toxic amblyopia with eventual optic atrophy resulting from drinking these adulterated "essences of Jamaica Ginger." In the light of subsequent knowledge it seems that these cases of death and blindness were due to methyl alcohol used in the illicit manufacture of the intoxicant rather than to any properties of the ginger.

Since it is evident that the recent outbreak of Jake Paralysis produced a polyneuritis it seems appropriate to cite several previous epidemics of polyneuritis all of which have in common with Jake Paralysis the fact that the toxic agent was carried as an adulterant in an alcoholic beverage.

Sir George Baker in an exceptionally interesting series of papers published in 1768 (4) discussed the etiology of the so-called "Devon-

shire Colic." For many years the inhabitants of Devonshire had suffered from this endemial malady, the chief symptoms of which were intestinal colic and palsy, particularly of the upper extremities. Former observers had quite definitely determined that the colic and palsy were connected in some way with the drinking of large quantities of the cider for which the county was famous. Baker recognized that the symptoms were those of lead poisoning and set himself to determine the mode of poisoning. He found that the presses and troughs in which the cider was made were lined with lead in Devonshire, whereas in the surrounding counties this was not the case. Chemical studies revealed that the cider from the Devonshire presses contained a formidable percentage of "saccharum Saturni" and that this was the cause of the colic and peripheral neuritis which had been epidemic in 1724 and endemic in the county since. Baker also related the occurrence of former epidemics of lead colic and palsy; the colic of Poitou which occurred as an epidemic in 1572 and raged for 60 or 70 years, and a similar epidemic in the duchy of Würtemburg in the latter part of the seventeenth century. He felt that these earlier epidemics were due to the adulteration of wine with litharge.

A much more recent epidemic of polyneuritis was reported by Reynolds (5, 6) in Manchester in 1900. The chief symptoms were paralysis of the muscles of the lower extremities, marked paresthesia, and peculiar keratosis and pigmentation of the skin, occasionally with herpes. The patients suffering from this neuritis all gave a history of drinking large quantities of beer. It was readily appreciated, however, that the type of the peripheral neuritis in these patients was different from that seen in the more common alcoholic neuritis. Careful chemical analysis of the beer sold in Manchester at the time revealed the presence of arsenic and a study of the material used in the manufacture of the beer showed that the source of the arsenic was sulphuric acid used in converting starch and cane sugar into glucose and invert sugar for brewing purposes.

III. ETIOLOGY AND PHARMACOLOGY

Miles and Goldfain (17, 18) are credited with recognizing the connection between the ingestion of "Jake" and the subsequent

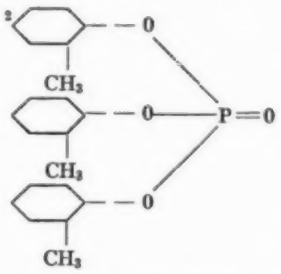
paralysis. "Jake" is a thin, dark-brownish liquid with an aromatic odor and a pungent taste. It was usually dispensed in 2 oz. bottles bearing the label "Fluid-extract of Ginger U. S. P.—alcoholic content 70 per cent," in addition to the name of the distributor. Valaer (9) points out, however, that the true fluid-extract of Ginger U. S. P. is unsuitable as an alcoholic beverage, being much too pungent and containing too much of the oleoresin of ginger. He stated that for years, and long before the advent of Prohibition, this "Jake" which was so popular as a beverage has not been the true Fluid-extract of Ginger of the U. S. Pharmacopoeia but an adulterated form in which more or less bland adulterants such as castor oil, molasses, glycerin, mineral oils and other substances have been substituted for most of the true oleoresin of ginger. As has been told, these adulterated beverages which consist mainly of alcohol (70 per cent), castor oil or some other bland adulterant and a sprinkling of the true oleoresin of ginger for flavoring have been very popular and thoroughly satisfying beverages. The "Jake" usually sold for about 35 cents a bottle and except in the hardiest drinkers the desired alcoholic affect could be obtained from just one or two bottles. Although ostensibly a drug and labelled as such, the "Jake" was used comparatively little as a medicine. The retailers procured the "Jake" either bottled or in bulk surreptitiously from unknown distributors or manufacturers and sold it to individual customers who more often than not mixed the "Jake" with a soft drink and drank it on the premises.

It is important to bear in mind that the consumption of "Jake" is not new and that it went on in not inconsiderable quantities even before the advent of Prohibition. It seemed evident then, that whatever caused the paralysis in these cases must have been some new adulterant, since many of the victims had drunk the "Jake" regularly for years and had had no previous symptoms. Because of the spontaneity of the outbreak and the widespread area involved, the logical conclusion was that some adulterant used in the manufacture of the "Jake" was the etiological agent. It was thought at first that the symptoms were caused by some denaturant in the alcohol but in a splendid pharmacological and chemical investigation Dr. Maurice I. Smith and his coworkers in the National Hygienic Laboratory showed

that the suspected "Jake" contained tri-ortho-cresyl phosphate and that this caused the paralysis.[2]

Valaer writes: "Tri-o-cresyl phosphate and rosin oil are ideal substitutes for oleoresin of ginger being soluble in alcohol and quite miscible with the true oleoresin that must be added if it is to be sold as Fluid-extract of Ginger. . . . . The result of these adulterants is a very cheap ginger, the tri-o-cresyl phosphate selling at about 30 cents a gallon."

To recapitulate: various adulterated but fairly harmless beverage gingers called "Jake" by the laity have been sold for many years as the Fluid-extract of Ginger U. S. P. These gingers were extensively used as intoxicants and consisted mainly of alcohol (70–80 per cent), castor oil or some other such adulterants and a small amount of the true oleoresin of ginger for flavoring. The substitution of tri-o-cresyl phosphate as an adulterant (surely without knowledge of its pharmacological effects), in order to undersell the castor-oil ginger, resulted in the epidemic of paralysis under consideration.



Technical Tri-cresyl phosphate is a bland, oily, non-volatile substance which looks much like mineral oil and is used extensively in industrial chemistry as a plasticizer. It is employed mainly in the manufacture of celluloid and allied products, in the tanning of leather and in making paints and varnishes. It is manufactured and marketed under the trade name of Lindol, or Lyndol. Until recently the technical Lindol has consisted mainly of tri-o-cresyl phosphate and only small percentages of meta and para compounds. Since the discovery of the toxicity of the ortho compound, the isomeric non-toxic meta and para esthers are substituted in the manufacture of Lindol. That the tri-cresyl phosphate was introduced into the manufacture of "Jake" purposely is evident, but it is equally evident that nothing was known of its pharmacologic effect.

IV. CLINICAL

a. History. The one common factor in the history of these cases is the antecedent ingestion of "Jake." The usual story is that the patient drank one or more two-ounce bottles of "Jake" which produced the desired alcoholic effect in a short while. Then, after a variable period (usually about two weeks), he first noticed a sensation of numbness, tingling, fatigue, or cramp-like pain in his calf muscles. This was not a marked sensation and usually caused no alarm. This peculiar cramp-like sensation in the calf muscles persisted one or two days, after which the patient noticed weakness of the legs which rapidly progressed into paralysis with "foot-drop" or inability to walk or to stand still. In the milder cases no further symptoms had become evident, but in most instances, about one week after the onset of paralysis in the legs, involvement of the upper extremities was noted. This first became noticeable because of the inability to perform the finer movements such as buttoning the shirt, lighting matches or holding heavy objects. The amount of involvement of the upper extremity varied from slight weakness of the intrinsic muscles of the hand to complete "wrist-drop." In almost all of these cases a very striking feature was the absence of pain as a symptom. The tingling numbness or cramp-like pain in the calves of the legs lasted only a day or two and was never very severe. The same was true of the pain in the upper extremity. A fact which has not been sufficiently emphasized is that the amount and severity of the paralysis vary directly with the amount of the adulterated ginger ingested. This is shown clearly in the experimental work cited later in this paper.

b. Physical Examination. On examination the chief findings were the paralyzed extremities. All of the patients showed the typical "foot-drop" of anterior tibial nerve injury (figs. 1 and 2). A characteristic "steppage gait" was noted in the ambulatory cases. The degree of paralysis varied from slight muscle weakness of the anterior tibial group of muscles with barely perceptible "foot-drop" to complete paralysis of all the muscles of the feet and legs and, in the most severe cases, paralysis of the muscles of the thighs. The paralysis was bilateral and symmetrical. In many, mild trophic disturbances were seen, cyanosis, hyperidrosis, coldness of the parts, or a shiny glistening skin.

Cutaneous sensory loss was never marked. Pain and temperature conduction were usually intact and tactile and vibratory sense were but slightly impaired. The ankle-jerks were absent in all of the patients. The other reflexes were inconstant. In most of the relatively mild cases the knee-kicks were exaggerated at first but later became normal or hypo-active; in the more severe, the knee-jerks became hypo-active or absent. The plantar response was uniformly flexor.

Compilation of the larger series in the literature shows that about three-fourths of the reported cases showed some involvement of the upper extremity. In the arm the degree of paralysis varied from a very slight weakness of the intrinsic muscles of the hand to almost complete paralysis of all the muscles of the hand and forearm (figs. 3, 4, 5, 6). In some of the more severe, the periosteo-radial reflex was absent but in most instances the reflexes were normal.

The cranial nerves were usually intact. There was no incontinence of urine or feces. No other systems of the body showed abnormalities.

c. Laboratory Examinations. No constant changes were noted. The blood and urine were usually negative. The cerebrospinal fluid showed an increased number of cells (up to 11 per cu. mm.) and slight increase in globulin content in some reports, but usually the fluid was normal.

d. Course. The usual course of the paralysis is one of rapid onset in the legs following a "pre-paralytic stage" of from 3 days to one month but usually about two weeks. Following the paralysis of the legs the involvement of the upper extremities becomes evident in about one week. The whole damage is done very rapidly and after several days there is no progression of the symptoms. The symptoms and signs of the paralysis become perfectly stationary and after two or three weeks all the sensory symptoms disappear and the patient is left with a flaccid, bilateral paraplegia or quadriplegia. Often there seems to be some improvement in the first few weeks but this is probably due to the education of the patient in the use of the affected limbs. In many of the more severe cases there is marked atrophy of the muscles, particularly of the interossei in the hands (figs. 3, 4, 5, 6) and the anterior tibial groups of muscles in the legs. In some, contractures have occurred. After a long time, usually 6 months or more, there is definite

improvement in the ability to use the hands and arms. There is said to have been improvement in the extensor movements of the feet and toes after intervals of from six to eighteen months from the onset. It is interesting to note that the improvement occurs in the reverse order to that in which the paralysis began. Thus the upper extremities, while they were involved last, recover first.

e. The Occurrence of Fatal Cases. There were very few fatalities that could be attributed directly to the poison. Vonderahe (37) reports one uncomplicated fatal case with a pathological study. This is abstracted here as worthy of comparison with the experimental findings.

A woman, aged 59, was admitted to the Hospital on March 27, 1930. She stated that in December, 1929, she was induced by a grocer to take Jamaica Ginger extract for a disturbance of the stomach, and that since that time she had taken one bottle daily except on Saturdays and Sundays when she usually took from two to three. On March 15, 1930, she began to notice weakness in the legs, with some cramping pains in the calves. This gradually became more severe and on March 27, complaining of inability to walk or to use her hands, she entered the hospital.

The patient was emaciated, but was mentally alert. The cerebrospinal fluid showed a faint trace of globulin, 2 cells, a negative gold curve and a negative Wassermann reaction.

She was able to speak, but tired quickly. It was possible to swallow solid foods with difficulty. The tongue protruded somewhat slowly and in the midline. There was inability to use the feet or the hands; a bilateral foot-drop and wrist-drop, with more pronounced weakness in the feet. The biceps, triceps, wrist, patellar, achilles and abdominal reflexes were present. There were no pathologic reflexes. Because of the weakness in the hands and feet, tests for coordination could not be satisfactorily performed. There was only a slight diminution of pain and light-touch sensation in the hands and feet, the borders of which were indistinct. The hands and feet were bathed in thin perspiration.

The woman's condition grew gradually worse. She developed incontinence of the bladder, followed in a few days by incontinence of the rectum. She gradually lost the ability to talk and to swallow solid foods, and later had extreme difficulty even in swallowing liquids. Respiration became difficult. She died on May 3, of respiratory paralysis.

These fatal cases, as compared with the usual type, are exceedingly rare and form a very small percentage of the total. It is interesting to note in the case reported above that the cumulative dose of the

tri-o-cresyl phosphate could easily have been 10 to 15 times the amount usually ingested and followed by mild paralysis.

f. Diagnosis. With the facts now known it seems almost impossible to confuse the symptoms caused by poisoning with tri-o-cresyl phosphate with any other condition. As it usually occurs, the malady is a clean-cut well-defined entity which shows the following salient features:

(1) The history of ingestion of "Jake," the adulterated fluid-extract of Jamaica Ginger, or of some other compound containing tri-o-cresyl phosphate.

(2) After a symptomless "preparalytic" stage of a number of days (usually about two weeks) the occurrence of tingling, numbness or cramping pain in the calves of the legs which lasts one or two days.

(3) Following the paraesthesias in the calves of the legs is the rapid onset of complete or partial paralysis of the extensor muscles of the toes and feet with variable degrees of paralysis and weakness but always with loss of the ankle-jerks.

(4) In about three-fourths of the cases there is a similar sudden onset of weakness or paralysis of the muscles of the hand and the extensor muscles of the forearm. This usually takes place about one week after the onset of paralysis in the legs.

(5) The paralysis is bilateral and involves both sides about equally.

(6) The course of the malady is chronic. Little improvement is noted for months after the onset. Finally, however, the weakness becomes less marked in reverse order to the way in which it began; that is, the muscles last afflicted are the first to resume function.

Before all this became so plain, however, it seemed necessary to differentiate this type of paralysis from numerous other conditions. Since it was evident that the poison, whatever it is, produces a polyneuritis, the various polyneuritides have to be considered:

I. Alcoholic Polyneuritis. This is a common form of polyneuritis. Pain and objective paraesthesias are usually marked. The onset is usually slower than in ginger paralysis. The knee- and ankle-jerks are usually absent. The paralysis seldom involves the upper extremities. Other signs of acute alcoholism, especially Korsakoff's syndrome, are frequently noted.

II. Lead Polyneuritis. The symptoms of lead palsy are usually

preceded by other symptoms of chronic lead poisoning (colic, blue line on the gums, anemia, and cachexia). The paralysis almost always appears first and is confined to the upper extremities; whereas in ginger paralysis the paralysis invariably occurs first in the lower extremities.

III. Arsenical Polyneuritis. Gastro-intestinal symptoms are rarely absent. Pain and paraesthesias are usual. Trophic disorders of the skin and diminution of cutaneous sensibility are common. The knee-jerks are almost always absent.

The other forms of toxic polyneuritis and infective polyneuritis seldom produce the purely motor type of paralysis seen in tri-o-cresyl phosphate poisoning.

g. Treatment. The treatment of these cases is similar to that used for all other cases of neuritis. After the ingestion of the poison has ceased, gradual improvement is dependent on rest, massage and mechanical supports to hold the extremities in good position and permit their use. The greater the patience and skill used, the better the result that may be expected. Return of function is very slow but continues gradually for many months.

V. EXPERIMENTAL

By administering samples of the confiscated Jake as well as synthetic tri-o-cresyl phosphate, Dr. M. I. Smith (7, 8) and others succeeded in producing a paralysis comparable to that seen in humans in a variety of laboratory animals (rabbits, chickens, dogs, calves and monkeys). Watkins (12) and Bowden and Turley (11) also produced weakness, ataxia and finally death in chickens after administering large quantities of the suspected ginger extracts.

The present authors then began their study which sought to reproduce the paralysis experimentally by injecting purified tri-o-cresyl phosphate subcutaneously into laboratory animals. It was then planned to study the effect of the chemical upon the tissues, particularly the nervous system. Cats were used in this work; there were fourteen in the series.

a. Reaction of cats to subcutaneous injections of tri-o-cresyl phosphates. It was found that all the animals into which the tri-o-cresyl phosphate was injected developed paralysis and in general three types of reaction were obtained.

If a fairly large dose (0.2 cc. per kgm. of body-weight) of the tri-o-cresyl phosphate was injected, the animal would remain entirely well for an interval of from 7 to 14 days. After this time the cat was seized with a rapidly ascending flaccid paralysis (exactly comparable to Landry's Acute Ascending Paralysis) which began always in the tail and hindlegs and rapidly increased to involve the muscles of the forelegs and trunk. Finally the animal died of respiratory (bulbar) paralysis 36 to 72 hours after the onset (see table I).

Second, if the smaller doses of the tri-o-cresyl phosphate were injected in either single or divided doses, the animals developed paralysis after a longer interval. At first only the tail would droop

TABLE I

The effect of single doses of tri-o-cresyl phosphate injected subcutaneously into cats

NUMBER OF EXPERIMENT	DOSAGE PER KGM. OF BODY WEIGHT	INTERVAL IN DAYS BEFORE ONSET OF PARALYSIS	INTERVAL IN DAYS UNTIL DEATH
	cc.		
1	0.5	10	3
2	0.5	10	2
3	0.3	11	34
4	0.2	7	1
8	0.185	7	9
11	0.07	14	1*
12	0.25	14	1

* Died of distemper.

and there was only a moderate ataxia in the hindlegs. The hindlegs grew weaker and more ataxic and in from 6 to 14 days the forelegs began to show some ataxia. Finally, after from 3 to 5 weeks the animals died either of a slowly ascending respiratory paralysis or from cachexia.

Table II shows the interval periods between the divided doses in the cats in this series. The first dose was near the lower limits of the amount required to produce paralysis. In the first three animals the interval time was not long enough to make it certain that the animals would remain well. The last two animals, on the other hand, were healthy for twenty-five days after the first injection and it is extremely probable that they would have remained normal if the administration

had not been continued. After the second fairly large dose in the first three cats, paralysis occurred uniformly after five days. The total interval time was twelve days, which is within the limits found after a single dose. The second interval time of five days was shorter than any after a single administration of the drug. This shortening of the second interval period is even more striking in the case of the last two cats; here it was decreased to three and four days. It appears obvious that the second dose must have augmented the action of the first, producing paralysis in a short time. These observations point toward a cumulative action of the tri-o-cresyl phosphate and indicate that it is eliminated very slowly, if at all. Another example makes this even clearer. An animal received a total of 0.125 c.c. per kilogram

TABLE II

The effect of divided doses of tri-o-cresyl phosphate in cats

NUMBER OF EXPERIMENT	1ST DOSE	INTERVAL	2ND DOSE	DAYS UNTIL ONSET OF PARALYSIS	DAYS UNTIL DEATH
	cc.		*cc.*		
5	0.01	7	0.1	5	1
6	0.1	7	0.1	5	1
7	0.1	7	0.1	5	1
9	0.1	25	0.1	3	24
10	0.05	25	0.05	4	2

of body-weight in five doses of 0.025 c.c. each. The five doses were injected at weekly intervals. Two days after the last injection the cat developed a typical ataxia of the tail and hindlegs which rapidly progressed to total flaccidity of the musculature of all four legs. It died of respiratory paralysis two days later.

Third, in one animal which received a total of only 0.1 cc. per kgm. of body-weight in 4 equal doses given at intervals of about 10 days there developed a definite ataxia of the hindlegs 5 days after the last injection. The animal showed the typical droop of its tail with ataxia of both hindlegs for about two weeks; after this time it rapidly began to improve and one week later was entirely well. This was the only cat in this series that showed improvement or recovery.

VI. PATHOLOGY

Only a few human autopsy reports are available in the literature and in only one of these autopsies was tri-o-cresyl phosphate the uncomplicated cause of death. The lesions, as would be expected from the clinical signs, are localized chiefly in the peripheral nerves and consist mainly in degenerative changes. There is no report of any inflammatory reaction anywhere in the nervous system. The lesions in the peripheral nerves consist in degeneration of the myelin sheaths and fibers as demonstrated by the Spielmeyer, Marchi, osmic acid, and fat stains. Vonderahe also reports similar degenerative changes in the anterior roots and marked changes in the anterior-horn cells. The changes in the anterior-horn cells consist mainly in swelling, chromatolysis, eccentric nuclei, shrinking and death of the cells. All sections of the neuraxis showed infiltration with amyloid bodies. In the fatal cases quoted above Vonderahe also reports: "Severe cellular changes similar to those found in the anterior-horn cells were noted in the hypoglossal nucleus, dorsal motor nucleus of the vagus and the nucleus ambiguus." He concludes: "The pathologic observations suggest a toxin which reaches the peripheral nerves in the extremities through the circulation, but which subsequently travels in the central nervous system along the nerve fibers and anterior roots. Thus in addition to the central chromatolysis in the motor cells of the anterior horn associated with involvement of the peripheral nerves, diffuse chromatolysis and death of the cells also occur. The toxin in severe cases may then make its way to the medulla where involvement of the vagal nuclei produces death by bulbar paralysis. There is an obvious tendency of the toxin to exert its pathologic effect most severely on the motor cells and fibers."

a. Results of Pathological Studies. All except three of the animals reported above were autopsied and blocks were taken from the nervous system and peripheral nerves for microscopical study. No gross lesions were discernible either in the viscera or in the nervous system except for the marked atrophy of the muscles of the legs in the animals which had been paralyzed for some weeks before death.

Study of the microscopic material from these animals does not show the very obvious changes that one would expect to be associated with

the degree of disability that was present; this is true of most cases of neuritis, regardless of the etiological agent. When there is no cellular infiltration associated with abnormal processes, the lesions that can be demonstrated microscopically are few. The abnormalities of the nervous system are pictured in the photomicrographs.

Particular attention in previous studies has been given to the peripheral nerves. Staining methods showed here such vagaries that emphasis in this work has been focused on the nerve roots in the lumbar and sacral regions. The Spielmeyer stain was used to demonstrate the myelin, and this stain also shows very clearly the neuro-keratin network in which the myelin is enmeshed. Figure 7 demonstrates the general decrease in myelin upon the fibers of the ventral root as contrasted with a dorsal root of one of the lumbar nerves. In normal cases, the ventral and dorsal roots, when examined under a low power of the microscope, appear to be myelinated equally. The toxin does not affect all the ventral root fibers to the same degree; this is true of most toxic processes involving the same region. Some of the neurones of a group having a similar location and similar physiological functions succumb far sooner than others. So, in the ventral root, the motor fibers are sparse and it appears that some have completely degenerated.

Six photographs, 9 to 14, show high-power views of the ventral and dorsal roots from a normal animal and from two that suffered from the paralysis. They are all stained by the same method and are photographed at the same magnification. The neuro-keratin shows particularly well in the pictures. With the fixation some shrinking and distortion have taken place but, in addition, the preparations show distinct differences that we believe may be attributed to the poison. A normal ventral nerve root is demonstrated in figure 9 and a normal dorsal root in figure 10. The ventral and dorsal roots may be readily distinguished. The axones in the ventral roots (fig. 9) are of two distinct sizes; the large axones are derived from the somatic motor cells of the anterior horns of the spinal cord and the smaller fibers with a thinner myelin sheath are preganglionic autonomic fibers. In the dorsal root (fig. 10), on the other hand, are fibers of varying sizes from the large axones to medium-sized, small and non-myelinated fibers. The unmyelinated axones are, of course, not demonstrated with this

stain. Figures 11 and 12 are from a cat which died of the paralysis after a relatively short period. A low-power comparison of the dorsal and ventral roots from this same preparation is given in figure 7. The dorsal root (fig. 12) shows no abnormalities. In the ventral root there is a general decrease in the number of fibers. In certain of those which are left there is a breaking-down of the myelin sheath and of the neuro-keratin network in which the myelin is enmeshed.

Figure 13 shows fibers of the ventral roots and figure 14 fibers from the dorsal roots in the lumbar region from a cat that exhibited a marked degree of disability and lived for about six weeks after the onset of the paralysis. The neuro-keratin and myelin sheaths in the ventral roots (fig. 13) are badly broken and disintegrated and no normal myelin sheath appears in the photograph.

Many of the axones in the dorsal roots of this same animal give signs of injury (fig. 14); the damage is not so marked as in the ventral roots where all the fibers are involved. In the dorsal roots the larger fibers appear to be more severely injured than the smaller. In human cases little sensory involvement has been demonstrated, but photographs will show abnormalities of the cells of the posterior root ganglia associated with the damage to the fibers.

A longitudinal section of a ventral lumbar root is photographed under high magnification in figure 8. Some of the fibers have normal myelin sheaths and neuro-keratin network, whereas in other cases the sheath is breaking up and is completely lost upon many of the axones.

Turning now to the spinal cord and the pathological condition of the cells, the picture again is a subtle one. All stages could be followed from the first loss of Nissl granules to the complete disintegration and loss of the anterior-horn cells. The autonomic neurones are much less severely affected than the somatic motor. This is shown in the low-power photograph of the anterior horn in the lumbar region (fig. 15). The central canal of the cord is seen at the extreme right and a group of autonomic cells at the left. The anterior horn lies in the center and lower portion of the picture. Although the autonomic cells are fairly well preserved, no somatic motor cells remain. The autonomic cells at this level do give evidence of some injury, as is demonstrated with the high power in figure 19; the only trace of somatic motor cells are the shadow forms illustrated in figure 20.

The first sign of damage in the somatic motor cells is a widening and enlargement of the region of the axone hillock which is normally free of chromphilic granules (figs. 16 and 17). This agranular area at the edge of the cytoplasm gradually increases in size and stains a bright greenish color. At about the same time a clump of heavily staining material appears at one edge of the nucleus. This is clearly seen in figure 18 and also in the cell on the left in figure 16. In many cases the nucleus migrates to the edge of the cytoplasm. Later there is a shrinking of the whole cytoplasm of the cell which comes to take a more or less homogeneous dark stain. The nucleus is the last portion of the cell to be lost and shadow cells may be recognized, although they are apparently not so conspicuous as in a human case which has previously been described. The interval between the development of paralysis and death was much longer in the human case than it was in any of the cats.

Although the autonomic cells are not injured as early or as seriously as the somatic motor, definite abnormalities are evident in figure 19. All the cells, and particularly the one in the lower portion of the photograph have undergone a loss of granules in the cytoplasm. The cell at the upper edge of the picture shows vacuolization of the outer portion of the cytoplasm.

Previously it has been stated that the sensory neurones were spared, and for this reason particular interest was given to the cells of the dorsal root ganglia of which examples are shown in figures 21 and 22. The nucleus of the cell in figure 21 has migrated to the outer edge of the cytoplasm and is surrounded by an area which is quite free from granules. Moreover, the capsule cells are embedded deeply in the cytoplasm of the cells, showing very evident neuronophagia. In figure 22 granules have disappeared from the edge of the cytoplasm. The larger cells of the posterior root ganglia have much greater evidence of injury than the small cells. Similarly, in the dorsal roots it is the large axones that show the disintegration of the myelin sheath. It has been suggested in previous work that many of the large axones in the dorsal roots carry impulses from the muscles and deep structures of the proprioceptive type. It perhaps is to be expected that these neurones of the sensory system would be the first to be attacked by the poison.

The tracts in the central nervous system are uninjured.

VII. COMPARISON OF GINGER PARALYSIS AND LANDRY'S ACUTE ASCENDING PARALYSIS

In 1859 Landry described a characteristic type of rapidly ascending acute paralysis, the symptoms of which were: the sudden onset following vague, prodromal symptoms of flaccid paralysis of the legs which rapidly ascends to involve the muscles of the pelvis, trunk, and upper extremities. All the tendon reflexes are absent. The paralysis then spreads cephalward to the muscles of deglutition, articulation and respiration, and death follows usually in a few days or weeks with symptoms of suffocation. In a very few cases the paralysis disappears in the reverse order to which it came and complete recovery follows. Sensory symptoms in all cases are slight. Landry emphasized the negative results of post-mortem examinations in all of his cases. He thought that the paralysis was caused by poisoning. Similar cases have been observed by neurologists everywhere since this description and all felt, as did Landry, that the symptoms were due to some sort of poisoning. Later investigations have revealed changes in the peripheral nerves and in the gray matter of the spinal cord at autopsy.

Oppenheim (34) wrote the following: "The cases which correspond exactly to Landry's type are clearly distinguishable clinically from other well-known diseases. Those which differ from this type for the most part closely resemble multiple neuritis, an affection which has in common with Landry's paralysis a toxico-infective basis. It is not, however, correct to identify the two completely and to regard Landry's paralysis as an extremely acute polyneuritis. Still less are we justified, we think, in regarding it as acute poliomyelitis, although with Raymond, who regards acute anterior poliomyelitis, polyneuritis, and Landry's paralysis as a morbid unity and as merely different manifestations of the same disease (*la cellulo-névrite aïgue antérieure*), we recognise its close genetic relationship." Many other observers have noted the similarity between Landry's acute ascending paralysis and multiple neuritis and some have thought that Landry's paralysis was merely a very acute peripheral neuritis in which the toxin finally invades the medulla causing death by bulbar paralysis.

In the recent epidemic of paralysis due to tri-o-cresyl phosphate poisoning, the sudden onset of flaccid paralysis in the legs, followed

in a few days by the involvement of the upper extremities, led many of the original observers to the conclusion that this type of peripheral neuritis was very similar to Landry's ascending paralysis but that it was less acute and that the toxin seldom reached the medulla to cause the bulbar symptoms. In the extremely interesting fatal case reported by Vonderahe (*vide supra*) a very large amount of the toxin was ingested. This was followed by severe paralysis of the extremities. After about six weeks paralysis of the muscles of deglutition and articulation was noted and seven weeks after the onset of the symptoms the patient died of respiratory paralysis. This case, it seems, corresponds very closely to the descriptions of Landry's ascending paralysis except that the course is not so rapidly progressive. It would seem then that the genetic relationship between Landry's acute ascending paralysis and this 1930 type of polyneuritis may be very close and that symptoms simulating Landry's paralysis are precipitated by a very large dose of the same neurophylic toxin which caused the epidemic of peripheral neuritis. Further evidence to support this view is that the symptoms and course of Landry's paralysis can be produced experimentally in cats by large doses of tri-o-cresyl phosphate.

VIII. DISCUSSION

Recently, in Germany, a number of cases of polyneuritis have followed the use of an abortifacient known as Apiol (40, 41, 42). The clinical and pathological findings were identical with those described in this paper. It has been demonstrated that Apiol contains tri-o-cresyl phosphate.

There are certainly many cases of polyneuritis found in man in which the etiological factor cannot be determined. In the present complex civilization poisons lurk in preparations on every hand and the toxic properties of many of them are not suspected. It is fortunate for the physician that the removal of these patients from their usual environment often produces a slow amelioration of the symptoms. One of these toxic agents has now been isolated and found to be tri-o-cresyl phosphate.

Experimental polyneuritis is in general very difficult to produce in animals with any of the poisons commonly causing this abnormality in

man. It is usually felt that some secondary factor is required in addition to the poison. Tiring the muscles upon a treadmill often augments the action of heavy metals and produces experimental paralysis. Tri-o-cresyl phosphate in sufficient doses always produces paralysis after the lapse of a latent period.

SUMMARY

This paper reviews recent observations upon an epidemic of polyneuritis, which followed the ingestion of Jamaica Ginger Extract adulterated with tri-o-cresyl phosphate, in 1930 and 1931.

The authors injected the pure tri-o-cresyl phosphate subcutaneously into cats and produced a marked paralysis in every case in which the dosage of the drug was adequate. There was always a definite latent period before the symptoms appeared. In the cats used, as in man, the caudal portion of the body was affected first and most severely and the paralysis then spread cephalward. By using divided doses of the drug given at fairly long intervals, it became evident that the effect of the drug was cumulative and that it was eliminated slowly, if at all. Further, the degree of paralysis varies directly, and the length of the latent period indirectly, with the amount of the poison given. If large doses of the purified tri-o-cresyl phosphate were injected the cats were suddenly seized with a rapidly fatal, flaccid paralysis exactly comparable to that described by Landry in 1859.

Pathological studies revealed lesions of the ventral roots of the spinal cord and of the somatic motor cells of the anterior horns. The autonomic cells were less severely injured. In a cat which survived for six weeks there was some injury of the large cells of the dorsal ganglia and fibers of the dorsal roots.

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PLATE I

These photographs were enlarged from a cinematographic film.

FIGS. 1 AND 2. Here is shown the foot-drop and the paralysis of the dorso-flexors of the ankle in a moderately severe case of "Jake" paralysis. The patient is quite unable to stand unless supported.

FIGS. 3 AND 4. The extensor musculature of the fore-arm is more severely paralyzed by the poison than the flexor. There is a wrist-drop. Atrophy of the flexor musculature is evident in both of the photographs.

FIGS. 5 AND 6. There is also atrophy of the intrinsic musculature of the hands seen in the thenar and hypothenar eminences and in the interossei.

5
6
3
4
1
2

PLATE II

FIG. 7. Low power photomicrograph of dorsal and ventral lumbar roots of a paralyzed cat, stained for myelin. There has been a loss of myelin from the ventral root fibers.

FIG. 8. Longitudinal section of a ventral lumbar root from a paralyzed animal. Some of the fibers show normal myelin and neuro-keratin network; others are completely disintegrated.

FIG. 9. Ventral root fibers of a normal cat stained for myelin. Large somatic motor and smaller autonomic fibers are present.

FIG. 10. Dorsal root fibers of a normal cat stained for myelin. The axones show great variations as to size.

FIG. 11. Ventral root fibers from the lumbar cord of a cat which was paralyzed for a relatively short time before death. Many axones have disintegrated and disappeared. Others show a degeneration of the myelin sheath.

FIG. 12. Fairly normal dorsal root fibers from the lumbar cord of a cat which was paralyzed a relatively short time before death.

FIG. 13. Ventral root fibers from the lumbar cord of a cat which was paralyzed for several weeks before death. The remaining fibers show marked disintegration.

FIG. 14. Dorsal root fibers from the lumbar cord of a cat which was paralyzed for several weeks before death. There is considerable damage of the axones, particularly of the larger ones.

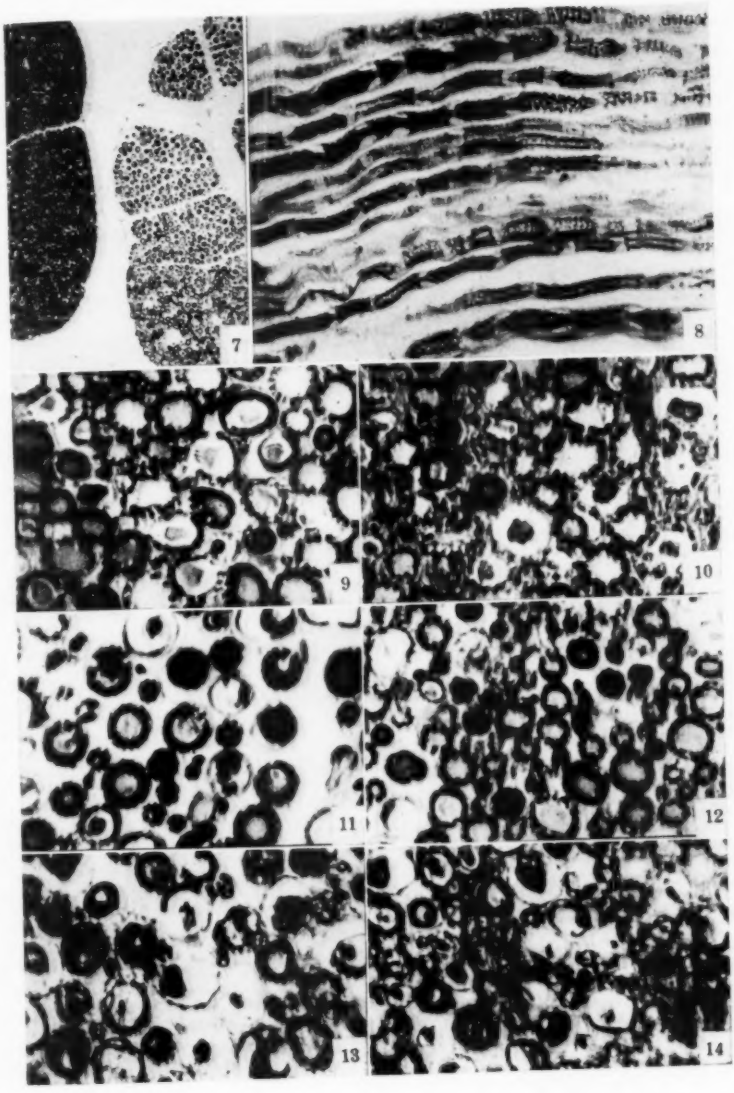
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PLATE III

FIG. 15. Low-power photomicrograph of anterior horn of the lumbar cord from a cat that was paralyzed. The central canal is on the right and a group of autonomic cells on the left. No somatic motor cells remain.

FIG. 16. One of these somatic motor cells shows a nucleus at the edge of the cytoplasm; the other an enlargement of the agranular area in the cytoplasm.

FIG. 17. There is an enlargement of the agranular area in this somatic motor cell.

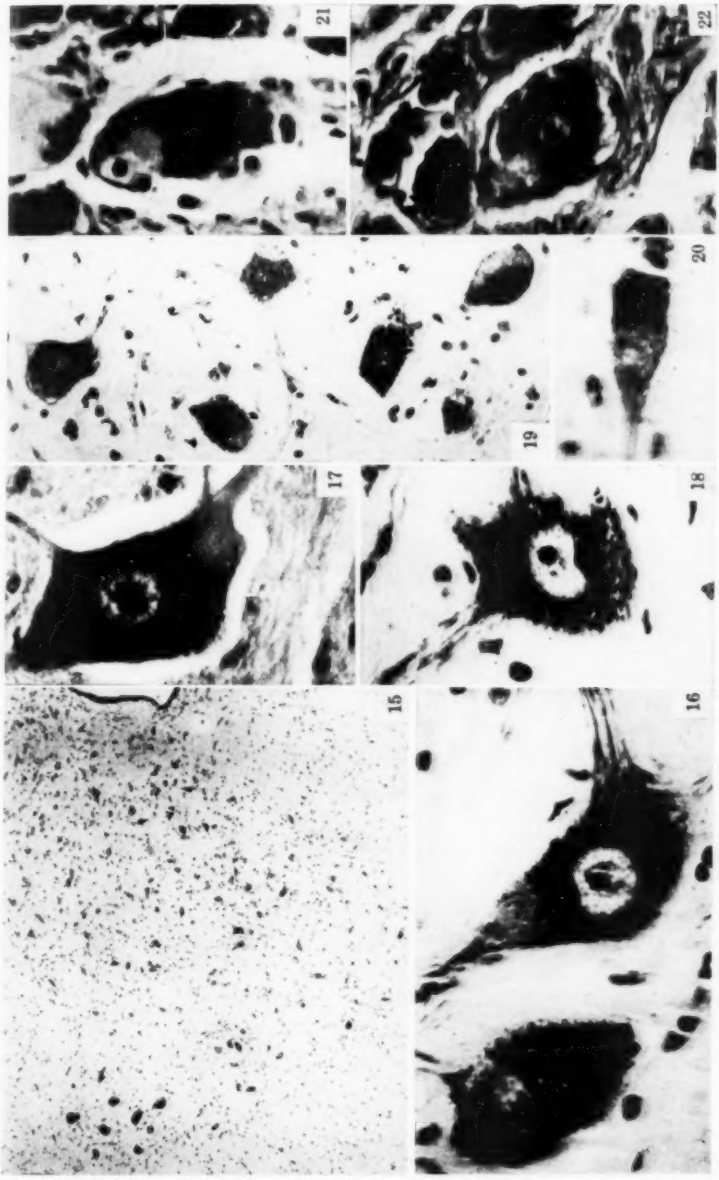
FIG. 18. A deeply staining area appears at the edge of the nucleus in many of the cells.

FIG. 19. The autonomic cells are not injured as severely as the somatic motor, but there is a loss of granules and vacuolization of the peripheral portion of the cytoplasm.

FIG. 20. The shadow forms are late stages in the disintegration of the anterior horn cells.

FIG. 21. Large cell from dorsal ganglion in the lumbar region of a paralyzed cat. The nucleus is at the edge of the cytoplasm and the area around the nucleus is agranular. The capsule cells are invading the cytoplasm.

FIG. 22. Another dorsal root ganglion cell demonstrates a loss of granules and neuronophagia.



UNIV. OF MICH.

FIVE CASES OF ADDISON'S DISEASE WITH SO-CALLED ATROPHY OF THE ADRENAL CORTEX

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In the past few years, the publications of a number of investigators have demonstrated a growing interest in those cases of Addison's disease in which the adrenal cortex is found at autopsy to be affected more or less selectively by a destructive process which is evidently non-tuberculous. The pathological lesion in the adrenal glands in such cases has been designated variously as atrophy (1), cytotoxic contraction (2), primary contraction (3), or as selective destruction of the suprarenal cortex (4). Although this peculiar lesion of the suprarenal gland ranks second only to tuberculosis as a cause of Addison's disease (3), its etiology is entirely unknown.

The literature from 1900 to 1929 on the subject of Addison's disease has been fully reviewed by Guttman (3). His analysis of 403 cases collected from this literature, pathological reports of which were available, shows that "primary contracted suprarenal gland" occurred in 65 cases or 16.13 per cent of the series. This proportion of the total, as Guttman remarked, probably gives a false impression of the relative frequency of this type of lesion, for the reason that cases of Addison's disease in which it was present have been reported frequently in recent years, while many cases of Addison's disease due to tuberculosis of the adrenal glands have probably failed to find their way into the literature. The tendency toward reporting these relatively rare cases of Addison's disease has continued to be in evidence. Since 1929, there have appeared in the literature reports of no less than 24 cases of Addison's disease in which an anatomical diagnosis of "atrophy" of the adrenal glands was reached after microscopic examination of the tissues (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). This seems to be a remarkably large number in comparison with the 65 cases reported in the preceding

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thirty years. However, a number of these cases were collected from autopsy records reaching back sometimes for long periods. This fact, considered together with the obviously increasing interest in this particular lesion of the adrenal glands, renders it impossible to be certain that this large number of recently reported cases offers any substantiation for the impression recorded by Wells (4) that Addison's disease due to "atrophy" of the suprarenal cortex is becoming more frequent.

Regarding this question, the significance of the experience in this laboratory is difficult to evaluate. During the past seven months, four cases of Addison's disease with "atrophy" of the adrenal cortex have come to our attention; during the same period no cases due to tuberculosis have been encountered. However, only two of these patients came to autopsy here. The other two died at home and reports of the autopsies with material for microscopic study were sent to Dr. G. A. Harrop, under whose care the patients had been in the Johns Hopkins Hospital. Examination of the records of this department showed that, prior to the occurrence of these recent cases, there had been, in a total of 12,342 autopsies, 12 cases of Addison's disease. Of these, ten showed tuberculosis of the adrenal glands and one presented dense scarring in the suprarenal region which, however, was not demonstrated to be tuberculous. The remaining case, which came to autopsy in 1901, showed typical "atrophy" of the adrenal cortex. It is not to be inferred that the recent cases of Addison's disease represent an increase in its incidence here. These cases have come to our attention primarily because of the interest of the clinicians in the disease and in its treatment. Even the fact that all of the four recent cases mentioned proved to be cases of "adrenal atrophy" may be no more than mere coincidence. However, it is suggestive of a possible increasing incidence of this rare lesion of the adrenal gland.

It was felt that the five cases of Addison's disease due to "atrophy" of the adrenal cortex formed a series worth reporting. Four of them are perhaps of added interest in that they had been treated with extracts of suprarenal cortex. The clinical features exhibited by these four patients have been discussed fully by Drs. Harrop, Weinstein and Marlow in a recent publication (15) and to them we are indebted for the clinical information preceding the pathological reports. Our cases 2, 3 and 4 correspond to those of the same numbers in their arti-

cle, while our case 5 corresponds to their case 8, the patient having died since their paper was written.

The case reports have been condensed as much as possible, only positive findings being recorded and detailed descriptions of commonplace lesions being omitted. However, some mention is made of *all* of the pathological conditions found in a careful study of all the material available. The limitations upon the study of each case are clearly indicated.

Case 1

Clinical history. F. W., a white boy 14 years of age, was admitted to the Johns Hopkins Hospital on July 23, 1901, suffering from typhoid fever, and died on July 29, 1901. He had been seen on three previous admissions to the hospital but prior to any of these he had had measles at the age of 2 years, whooping-cough at the age of 5 years, scarlet fever at the age of 7 years, and chills and fever at the age of 8 years. On his first admission to the hospital in April, 1896, he complained of chills and fever, and a diagnosis of double tertian malarial fever was made. At that time, an extraordinary pigmentation of the skin was noticed. The skin was described as being of a dusky hue with definite bronzing over the backs of the hands and wrists. The mother stated that the peculiar colour of the skin had appeared about 1893, when the patient was 6 years old and at least two years prior to the appearance of any symptoms of malaria. However, a diagnosis of Addison's disease was not made until the second admission in February, 1897, when the patient came into the hospital suffering again from tertian malarial fever. On this occasion the colour of the skin was about the same as on the previous admission. The mother said that the boy had always been active and had experienced no symptoms of gastric or intestinal irritation. The patient was seen again in September, 1899, when the skin was described as being of a uniform light brown colour. On the final admission in 1901, the patient had symptoms and signs typical of typhoid fever which had a fatal outcome within a few days. The pigmentation of the skin was generalized over its whole surface but intensified over the neck, the hands, the scrotum, and the legs just below the knees. Pigment was seen also on the mucous surfaces of the lips and on the gums about the upper and lower incisors. The final clinical diagnosis was typhoid fever and Addison's disease.

Autopsy (No. 1768). A complete post-mortem examination was made one hour after death by Dr. Eugene L. Opie.

The anatomical diagnosis was as follows: Addison's disease; so-called "atrophy" of the adrenal cortex, with lymphocytic infiltrations in the cortex and medulla; pigmentation of the skin. Typhoid fever; hyperplasia and beginning ulceration of Peyer's patches and the solitary follicles of the ileum; hyperplasia of the mesenteric and retroperitoneal lymph nodes. Acute splenic tumor. Typhoid necroses in the liver. Early biliary cirrhosis of the liver. Tuberculosis of mediastinal lymph node.

The following notes were made from the autopsy protocol and from a microscopic study of fresh sections cut from the tissues of this case which were found to be quite well preserved after more than thirty years. Unfortunately, the thyroid gland was not available for study.

With the exception of the liver and adrenal glands, the organs showed only the lesions usually associated with typhoid fever.

Sections of the liver showed, in addition to typhoid necroses, a considerable increase in the fibrous tissue about the portal areas and these regions were infiltrated by large numbers of lymphocytes and large mononuclear cells.

The thymus gland was not enlarged and it was normal microscopically.

Adrenal glands. The adrenal glands were found at autopsy only after the most careful search, which revealed a small mass of atrophic adrenal tissue on each side. These together weighed 2.2 grams. They were flattened triangular bodies, the left measuring $2.5 \times 1.5 \times 0.3$ cm. and the right $3.5 \times 2.0 \times 0.2$ cm. Both of them were almost wholly grayish in colour and fibrous in consistency but on their surfaces were a number of small rounded grayish-brown nodules the largest of which measured 3 mm. in diameter. On section the tissue was tough and grayish-white in colour except for the brownish nodules described which were all that could be identified as cortical tissue.

Numerous microscopic sections cut from the two adrenal glands presented very similar pictures. In all of them the histological structure of the medulla was well preserved, although in several sections it contained a few scattered focal accumulations of lymphocytes. Large areas of the cortex had disappeared completely, leaving only a thin layer of loose fibrous connective tissue which thus formed an encapsulating sheath for the medulla. This layer was quite thin and delicate and apparently was composed of the collapsed framework of the cortex. It contained a moderate number of lymphocytes, diffusely distributed. The few remnants of cortical tissue that were seen in the sections presented a variegated appearance. In some areas a vestige of the normal structure of the cortex could be made out through the presence of groups of cortical cells arranged in small rounded clumps simulating the appearance of the zona glomerulosa. Sometimes a few shrunken cells were seen within this zone but in none of the sections were the fasciculate or reticular zones left intact. Further evidence that the outermost layer of the cortex was the last to disappear was furnished by the observation that cortical cells in fairly typical glomerular arrangement were often seen separated from the medulla by a thin layer of loose, vascular fibrous tissue which was taken to represent the collapsed framework of the inner zones of the cortex. Other groups of cells in similar positions in relation to the medulla were arranged in an apparently haphazard manner. In such areas there were marked cellular changes. Some of the cells were large and swollen in appearance, sometimes with large deeply staining nuclei, while other cells were small and shrunken with granular cytoplasm and very palely staining nuclei. The supporting tissue in the neighborhood was very vascular and infiltrated with considerable numbers of lymphocytes. In still other situa-

tions larger groups of cortical cells were seen arranged in clumps interposed between the layers of the delicate fibrous sheath which surrounded the medulla. These masses of cells were rounded in outline and had the appearance of islands of regenerated tissue which had grown and expanded in an outward direction so that they formed small nodular protuberances on the periphery. The cells composing these nodules were packed in a solid mass bearing no resemblance to the normal architecture of the adrenal cortex. The individual cells varied considerably in size, some being quite large, but they seldom showed any degenerative changes. Lymphocytes, though often numerous in the supporting tissue about the regenerated nodules, were never present in large numbers among the cells composing them. In every instance, the capillaries and fine vessels in these nodules were widely dilated and packed with red blood cells giving the appearance of great vascularity.

Case 2

Clinical history. M. S., a white married woman, 37 years of age, was first seen in the Johns Hopkins Hospital in February, 1930. At that time she complained of weakness of two years' duration. She had experienced a gradual loss of energy for four or five years before the onset of definite symptoms. Her systolic blood pressure was reported to have been 95 mm. of mercury in 1928 and during that year her skin had begun to darken. On examination in 1930, there was found a moderate diffuse brownish pigmentation of the skin in typical distribution with pigmented areas also on the gums and buccal mucosa. Her blood pressure was 98 systolic and 65 diastolic. A diagnosis of Addison's disease was made. Treatment with extract of suprarenal cortex was commenced in July, 1930 and continued until November, 1930, with definite subjective but not much objective improvement. The patient was not seen again until April, 1931. During the interval she had experienced increasing weakness and the pigmentation of the skin had become decidedly deeper. The blood pressure was 70 systolic and 50 diastolic. She was admitted to the hospital and shortly afterward passed through an acute attack of suprarenal insufficiency followed by two milder attacks in May, 1931. All of these were successfully treated with injections of cortical extract and intravenous glucose. After discharge from the hospital at the end of July, 1931, the patient was given an injection of cortical extract twice a week and continued in excellent condition with the exception of one relapse of moderate severity in October, 1931. She came to the dispensary on January 15, 1932, for her bi-weekly injection of cortical extract. Her general condition was good; the blood pressure was 76 systolic and 54 diastolic. The following day she ate a rather heavy mid-day meal which was followed by a mild gastric upset. During that night she complained of some shortness of breath and pain about her heart. She was drowsy the next morning and remained in bed where her husband found her dead at noon.

Autopsy (No. 12380). The post-mortem examination was performed five hours after death under conditions of peculiar difficulty in the bedroom of a private house. Permission to examine the cranial contents was withheld.

The anatomical diagnosis was as follows: Addison's disease; so-called "atrophy" of the adrenal cortex; pigmentation of the skin. Lymphocytic infiltrations in the adrenal medulla, thyroid gland and kidneys. Enlargement of Peyer's patches and the solitary follicles in the ileum and of some retroperitoneal lymph nodes. Atrophy of the ovaries. Fresh fibrinous pericarditis. Small pleural scars at apices of both lungs; old pleural adhesions (right).

The visceral and parietal surfaces of the pericardium were covered by a thin layer of fresh fibrinous exudate which contained a few polymorphonuclear leucocytes and lymphocytes. Sections stained to demonstrate bacteria failed to show any organisms.

The thymus gland was not enlarged.

The thyroid gland was normal in its general features but it contained numerous dense, rounded accumulations of lymphocytes, some of which resembled lymphoid follicles with definite "germinal centres." These encroached upon and partly replaced the acinar tissue in their immediate vicinity. In addition there was a more diffuse scattering of lymphocytes throughout the gland.

The kidneys were found microscopically to contain numerous dense clumps of lymphocytes in the interstitial tissue just beneath the capsule and a few accumulations were seen deeper in the cortex. The tubules in the neighborhood were usually small and shrunken and their basement membranes were often thick and hyaline. In one kidney a dense focal accumulation of lymphocytes was found in the wall of the pelvis.

The ovaries were small and shrunken and there was a complete absence of Graafian follicles.

Adrenal glands. At the time of autopsy the adrenal glands were not to be seen. However, a careful dissection of the retroperitoneal tissue after fixation, revealed a small body on each side, which on microscopic section proved to be adrenal gland. These masses were of about equal size and after Zenker fixation each one measured about $15 \times 8 \times 2$ mm. They were both flattened bodies of slightly irregular outline consisting of a central mass which became thinned out at the margins to a mere membrane. They were of a dark brownish-gray colour, both externally and on the cut surface. Neither of them contained any tissue suggestive of adrenal cortex.

Numerous microscopic sections were made from these bodies and all of them presented a similar picture. The medulla was clearly recognizable and well preserved in its histological structure but the branching strands of medullary cells were separated by a connective-tissue network which was distinctly denser than normal. Here and there in the medulla were small focal accumulations of lymphocytes arranged in rounded groups. In a few small areas the lymphocytic infiltration was present in a more diffuse distribution. Cortical cells were completely lacking in all of the sections. The medulla was surrounded only by a thin and delicate sheath composed of flattened cells. In many of the sections, this sheath extended for some distance beyond the margins of the medulla at either end as a thin membrane. Fine blood vessels were numerous between its layers, but it contained no cortical or medullary cells.

In this case the masses of tissue which proved to be the remains of the adrenal glands were dissected rather closely and it seems possible that a few cortical cells might have been found if the sections had included more of the surrounding tissue. However, if such were the case, they must have been extremely few in number since there was nothing in the gross examination to suggest that any part of the adrenal glands had been missed in dissecting them out.

Case 3

Clinical history. E. S. B., a white married man, 34 years of age, was first seen at the John Hopkins Hospital in April, 1931. He complained of a generalized weakness which had developed insidiously since August, 1930. Darkening of the skin had been noted first in February, 1931. On examination in April, the skin was everywhere of a pale brown colour which was intensified over the face, the backs of the hands and forearms, and over the ventral surface of the torso. A triangular area of deeper pigmentation was present over the lumbo-sacral region and the perineum was also deeply pigmented. The blood pressure was 105 mm. of mercury systolic and 55 diastolic. A diagnosis of Addison's disease was made and the patient was admitted to the hospital. Shortly afterward he had an acute relapse with severe nausea and vomiting, general abdominal pain, marked weakness and falling blood pressure. He was treated with extract of suprarenal cortex and intravenous glucose and showed marked improvement within a few days. He was kept under treatment and observation in the hospital until July, 1931, and then was allowed to go home. During the summer he received one injection of cortical extract daily and continued in excellent condition. He returned to the hospital for observation for a short period in October, 1931. The pigmentation of the skin was if anything a little paler than before. The blood pressure averaged 88 systolic and 55 diastolic. He returned to his home apparently in good condition. However, ten days later he developed anorexia and irritability, and although he was reported to have improved somewhat after injection of larger doses of cortical extract, he died on the fifth day (November 13) in an attack of coughing and dyspnoea which the attending physician thought similar to asthma and which was relieved somewhat by injection of adrenalin.

Autopsy. The post-mortem examination was performed by Dr. Earl Clarke of Providence, R. I., to whom we are indebted for the information regarding his findings and for microscopic sections of the organs examined. The autopsy permission limited the examination to the abdomen.

None of the abdominal organs, with the exception of the adrenal glands, showed any gross lesions. Microscopic sections of the liver were not available for study but of the other abdominal organs only the kidneys were remarkable.

Small areas of the kidney cortex just beneath the capsule were seen to contain interstitial accumulations of lymphocytes which were sometimes quite dense. The tubules near these areas were curiously shrunken in appearance and their basement membranes were often conspicuously hyalinized.

Adrenal glands. At the time of autopsy the retroperitoneal tissue was carefully searched but the adrenal glands could not be found. However, in microscopic sections of tissue removed from the suprarenal region, one adrenal gland was identified. There was a complete absence of cortical cells and only the medulla remained intact. Throughout its extent there were numerous thin fibrous strands interposed between the groups of medullary cells. The tissue was infiltrated here and there with dense clumps of lymphocytes. In one area the lymphocytic infiltration extended for some distance in a narrow zone along the periphery of the medulla. In other situations lymphocytes were present in smaller numbers and were more diffusely distributed. However, large areas of the medulla were entirely free from lymphocytes and except for the increase in the density of the stroma these areas appeared normal.

Case 4

Clinical history. R. M. C., a white married woman, 36 years of age, first noticed weakness six months after her first pregnancy in 1923. Early in 1927 her blood pressure was reported to have been 95 systolic and 62 diastolic, and in September of the same year a diffuse brown pigmentation of the skin was observed. From that time until June, 1931, she experienced recurrent attacks of weakness and nausea and there was a steady loss of weight. The patient was then admitted to the Massachusetts General Hospital where she suffered a rather severe relapse. However, she showed marked improvement after treatment with large doses of extract of suprarenal cortex. The injections were discontinued on September 23, and for a time she did well without them. On October 28, 1931, the patient was transferred to the Johns Hopkins Hospital. At that time there was a typical diffuse brownish pigmentation of the skin and slight buccal pigmentation. The blood pressure was 100 systolic and 60 diastolic. A relapse occurred shortly after admission to the hospital but subsided under treatment with cortical extract and after the removal of two badly infected teeth. On November 9, jaundice was first noted and this steadily increased. The patient had a series of episodes, each lasting for several days, in which there was severe nausea, anorexia, vomiting and stupor. There was marked hypotension and a considerable secondary anaemia developed. During the last days of life, oedema of the legs and ascites appeared, and there was bleeding from the gums. The patient died December 29, 1931. The final clinical diagnosis was Addison's disease, mediastinal tumour, and subacute "yellow atrophy" of the liver.

Autopsy (No. 12343). A complete autopsy was performed two hours after death.

The anatomical diagnosis was as follows: Addison's disease; so-called "atrophy" of the adrenal cortex and partial destruction of the adrenal medulla; pigmentation of the skin. Lymphocytic infiltrations in the adrenal glands, kidneys, pancreas, voluntary muscle, thyroid gland and meninges. Partial destruction of the hypophysis, with round-cell infiltration. Atrophy of the ovaries. Peculiar cirrhosis

of the liver; jaundice; anasarca. Mediastinal tumor in the thymus region with cyst formation.

The mediastinal tumor formed a flattened mass which lay over the anterior wall of the pericardium. It measured $10 \times 9 \times 4$ cm. In it there were a number of cyst-like cavities which were filled with dark brown fluid and caseous material. Microscopically, it was composed largely of lymphocytes and there were condensations of cells which resembled germinal centres. However, no Hassall's corpuscles could be identified. The capsule was thick and fibrous and there was a great deal of fibrous tissue in the tumor itself. The large cystic spaces were filled with an amorphous caseous material in which cholesterin crystal clefts and fat-laden cells were numerous.

The liver was scarred and shrunken, weighing only 800 grams. Microscopically, it showed a most extensive and apparently progressing cirrhosis which was most pronounced in the periportal areas where regenerating bile-ducts were frequently seen. The liver parenchyma was greatly reduced, often being represented only by scattered islands of tissue. Even these were frequently the site of fresh necroses which were infiltrated by numerous lymphocytes and large mononuclear cells.

The cortex of both kidneys, while showing no structural change, contained frequent interstitial accumulations of lymphocytes.

Small scattered aggregations of lymphocytes were found also in the interstitial tissue of the pancreas and in the rectus abdominis muscle.

The thyroid gland was normal for the most part but one good-sized collection of lymphocytes was found in the interstitial tissue just beneath the capsule.

In the meninges there were scattered accumulations of small round cells, especially near the blood vessels.

The hypophysis contained a small focal area of atrophy in the anterior lobe, in which large and small mononuclear cells were numerous.

The ovaries were somewhat scarred and only a very few Graafian follicles could be found.

Adrenal glands. The adrenal glands were not to be seen at the time of autopsy, but they were subsequently found in tissue removed from the suprarenal region. Both of them were very small flattened bodies of rounded outline which together weighed approximately 5 grams. That on the left side measured about $2.3 \times 1.2 \times 0.1$ cm. and that on the right, about $3.5 \times 2.5 \times 0.1$ cm. No cortical tissue could be identified in the gross but a central mass of dark brown friable tissue suggested adrenal medulla.

Numerous microscopic sections were cut for study. In both adrenal glands a good proportion of the medulla remained intact. In many places the cells were plump and the medulla did not appear to be greatly altered, but in other situations the fibrous connective-tissue framework was definitely denser than normal. Many areas were densely infiltrated by large and small mononuclear cells and in these localities the medullary cells were shrunken and many had disappeared. Other parts of the medulla were reduced to a thin strand composed largely of loose vascu-

lar connective tissue in which only occasional medullary cells remained. In the right adrenal gland, no cortical cells were found. The medulla was surrounded only by a loose fibrous connective-tissue sheath in which there was a moderate number of lymphocytes. Many sections of the left adrenal gland presented a similar picture, but in some of them remnants of the cortical layers could be clearly distinguished. Sometimes all three zones of the cortex could be recognized but more frequently the reticular layer had disappeared and only the fasciculate or the glomerular zone remained. Remnants of the zona glomerulosa were perhaps most frequently spared, although the fasciculate layer sometimes persisted after the other two had disappeared. In other areas, small groups of cells remained but were too much distorted to permit of identifying them as remnants of any single layer of the cortex. The majority of the cortical cells which could be distinguished as such were normal in appearance. However, some of them about the periphery of clumps of normal-looking cortical cells were shrunken, the cytoplasm was very granular, and the nuclei stained poorly or not at all. In such areas lymphocytes were very numerous and indeed all parts of the cortical remnants were more or less densely infiltrated by large and small mononuclear cells, the latter predominating. The sections showed no evidence of regeneration of cortical cells.

Case 5

Clinical history. M. D., a white unmarried woman, 35 years of age, was first seen at the Johns Hopkins Hospital in July, 1931, and at that time complained of weakness, loss of weight, pigmentation of the skin, anorexia and urticaria. Pigmentation of the skin had been noticed first four years prior to her admission to the hospital, but weakness and loss of weight had become marked only in the last fifteen months before admission. During the last six months of this period the patient had been confined to bed because of marked asthenia. Nausea and vomiting had occurred daily for about two months. Her temperature had been very low and her systolic blood pressure was reported to have fluctuated between 60 and 90 mm. of mercury. Loss of weight and anorexia continued and the pigmentation of the skin became deeper. On admission to the hospital the patient was very emaciated. There was a diffuse reddish-brown pigmentation of the skin intensified about the eyes and over exposed areas, along the skin folds, about the nipples and over the knees. There were also large areas of leukoderma over the neck, abdomen, back and legs. The blood pressure was 92 systolic and 70 diastolic. Treatment with extract of suprarenal cortex was instituted, but three weeks after admission a severe relapse occurred which, however, finally subsided after treatment with large doses of cortical extract and dextrose, administered intravenously. From that time onward the patient received injections of cortical extract twice daily. She was discharged in October, 1931, and was able to carry on restricted activities. She returned to the hospital for observation in January, 1932, and appeared to be in good condition, but the weight, blood pressure and pig-

mentation were unchanged. She returned to her home and continued to receive supplies of cortical extract. Detailed information is lacking regarding the events leading up to her death which occurred on May 1, 1932.

Autopsy. The post-mortem examination was made by Dr. H. H. Plowden of Columbia, S. C., to whom our thanks are due for a report of his gross findings and for blocks of tissue from the organs mentioned below. Only the abdominal contents were examined.

Several mesenteric lymph nodes were reported to have been somewhat enlarged, but none of the abdominal organs with the exception of the adrenal glands showed any gross lesions.

Microscopic sections of the mesenteric lymph nodes revealed no lymphoid hyperplasia.

In the sections of spleen the Malpighian bodies were well developed but the organ was essentially normal.

The liver showed marked shrinkage and atrophy of the liver cells about the efferent vein of each lobule.

Sections of the pancreas and of one kidney revealed no abnormality.

Adrenal glands. The right adrenal gland could not be found at autopsy, but the left adrenal was discovered and was sent to us intact. It measured $2 \times 0.9 \times 0.2$ cm. It was enveloped in a loose fibrous capsule which enclosed a central mass of dark brownish-gray tissue. The appearance of the latter suggested adrenal medulla but no cortical tissue could be definitely identified.

Numerous microscopic sections were cut. In all of them the medulla was intact but its cells were rather shrunken in appearance and there was a definite increase in the density of the fibrous connective-tissue framework. It contained numerous rounded accumulations of lymphocytes. In many places the medulla was in direct continuity with a loose vascular fibrous connective-tissue sheath, but in other areas small numbers of cortical cells separated the two. These cortical cells were usually isolated or in groups of two or three so that it was impossible to determine of which cortical zone they were remnants. Many of these cells were swollen and granular with pale-staining nuclei and some groups were completely necrotic. The areas in which these cells persisted always were infiltrated more or less densely by lymphocytes and sometimes small haemorrhages were present with a few scattered granules of iron-containing pigment. In each section a few larger clumps of cortical cells were seen interposed between the medulla and the capsule. However, the arrangement of these cells bore no resemblance to the normal architecture of the adrenal cortex. They were packed in solid masses of rounded or oval outline which appeared to be islands of regenerated cortical tissue. There was great variation in the size of the cells and the largest of them often possessed very large hyperchromatic nuclei. Such nodules of cortical cells were often surrounded by a moderate infiltration of lymphocytes, but their central parts were remarkably free from infiltrating cells.

DISCUSSION

All of the cases here reported, and particularly the last four, lend support to the now generally accepted idea, that it is chiefly the deficiency of the adrenal cortex rather than any change in the medulla which is responsible for the clinical syndrome of Addison's disease. Nevertheless, there still remains the possibility that the relatively minor alterations in the medulla may be partly responsible for some of the clinical manifestations of the disease, and especially for the lowering of the blood pressure. However, the existence of such a relationship is not supported by the evidence gathered from this study. Cases 2, 3 and 5 exhibited hypotension of a degree quite common in Addison's disease, although the adrenal medulla was only slightly altered histologically. Case 4 showed much more severe damage to the medulla than did any of the others and yet the patient's blood pressure, as recorded during the period of observation here, did not differ appreciably from the pressures recorded in the other cases. A relationship between the severity of the symptoms and the amount of remaining adrenal cortical tissue is not evident among the last four cases, nor can it be said that the presence of cortical regeneration in Case 5 had conferred any advantage upon this patient as compared with Case 4 in which no evidence of cortical regeneration was found. On the other hand, in Case 1, cortical tissue was much more abundant than in any of the others and the symptoms of the disease were proportionately mild; cortical regeneration was active and the time interval between the appearance of skin pigmentation and death was several years longer than in the other four cases. Indeed, the patient evidently had suffered no disability and eventually died of typhoid fever. Probably the patient's age of 14 years was of some importance in relation to the activity of regeneration and to the longer survival period.

The pathological changes in the adrenal glands corresponded very well with those which have been described by others and which are well summarized by Guttman (3). Only in Case 1 was cortical tissue clearly distinguishable in the gross examination and then it was present in the form of regenerated nodules. Microscopic examination showed either complete loss of the original cortical layers or such widespread destruction that they were represented only by small remnants.

Study of the sections showed distinctly that the zona reticularis disappeared first. Of the other two layers, the zona glomerulosa usually persisted longer, although the cells of the fasciculate layer sometimes were present after the other two layers had disappeared. When regeneration of cortical tissue was in evidence, the islands of regenerated cells always formed the major portion of the total cortical tissue. The process of destruction of cells consisted of a progressive diminution in the depth of staining of the nuclei with accompanying granulation of the cytoplasm until the cell outlines were lost completely. In one case there were small haemorrhages in the cortex in the areas undergoing destruction. The apparent increase of fibrous tissue in the cortex was no more than could be readily accounted for by the collapse of the supporting fibrous framework. The medulla usually showed some increase in the density of the fibrous stroma and sometimes the medullary cells were slightly shrunken in appearance. More or less dense and abundant infiltrations of lymphocytes were always present in the adrenal medulla and among the remnants of cortical tissue. This process of necrosis of cortical cells with slight relative fibrosis and the presence of lymphocytic infiltrations in the cortex and medulla have been almost constant findings in the experience of others.

Other than the lesions in the adrenal glands and the pigmentation of the skin, no changes were found constantly in other parts of the body. Even the lymphocytic infiltrations in various situations were not always present except in the adrenal glands themselves. In only two cases was the thyroid gland available for study and although numerous dense lymphocytic infiltrations were present in one instance, only one comparable accumulation of lymphocytes was found in the other. In three of the five cases, interstitial lymphocytic infiltrations were present in the cortex of the kidneys often associated with changes in the neighboring tubules. The small accumulations of lymphocytes found in case 4 in the pancreas, voluntary muscle, meninges and hypophysis, were not repeated in any of the others. Hyperplasia of lymphoid tissue was not by any means a feature of our cases. Excepting case 1, in which the lesions of typhoid fever were present, there was found a slight enlargement of Peyer's patches and of some of the retroperitoneal lymph nodes in only one case. The thymus gland was examined in three cases and in two of them it was not enlarged. The

tumor in the thymus region in the remaining case was believed to be of no significance in this connection. No lesions were found in the last four cases which could be attributed to any deleterious effect of the treatment with extract of suprarenal cortex. The same has been true of other cortin-treated cases, pathological reports of which have appeared recently (11, 12, 14).

As we have already stated, the cause of the lesions in the adrenal glands is quite unknown. There was no evidence in our cases that tuberculosis had played any part in the process. There was nothing to suggest a syphilitic origin and, moreover, in the last four cases the Wassermann reaction was negative. In spite of the cellular infiltrations the pathological picture was not characteristic of a chronic inflammatory reaction. In none of the cases were the adrenal vessels narrowed or occluded and it is quite evident that the process was not one of true atrophy. On the other hand, all of the evidence is consistent with the conception that some destructive agent, acting more or less specifically upon the adrenal cortex, was responsible for the necrosis of cortical cells, a process which continued in spite of regenerative efforts until the surviving cortical tissue was too scanty in amount to support life. The nature and origin of the destructive agent is a matter for speculation. Kovács (2) believed that a cytotoxin elaborated through faulty metabolism might be responsible, and the toxins of infectious diseases have been suggested. Wells (4) compared the lesions in the adrenal glands with "acute yellow atrophy" of the liver, and suggested the probability that unknown toxins of a similar nature were responsible for the necrosis in both instances. In this connection it is interesting that one of our cases presented widespread cirrhosis and fresh necrosis of the liver, while another showed a definite increase in the fibrous tissue about the portal areas of the liver lobules. However, the presence of liver damage in cases which show the adrenal lesions under consideration is too rare an occurrence to permit of placing much significance upon their association. All things considered, it seems most likely that the adrenal lesions are due to a circulating toxin, but up to the present time, its origin and nature have remained obscure and its very existence is still hypothetical.

It was thought that a search of autopsy material might bring to light some cases in which a similar process of destruction in the adrenal

gland might be found in its early stages or in a state of quiescence. We were able to find four such cases (nos. 9123, 12097, 12318, 12557), which clinically had shown no symptoms or signs of Addison's disease but in which the adrenal glands were altered in a most interesting way. In all of them, one or both of the adrenal glands had presented more or less marked thinning out of the cortex in localized areas. Microscopic examination showed a loss of the reticular layer in these areas and in three of the cases the fasciculate zone had disappeared also in many places so that the zona glomerulos was all that remained to represent the cortex. In the fourth case, the reticular and the glomerular zones were the ones most widely affected, while the fasciculate zone was left for the most part intact. However, in all of the cases, there were some localized areas where the whole thickness of the cortex was disorganized, leaving only a few distorted cortical cells lying in the collapsed stroma, and in one case, one end of the adrenal gland was reduced to a thin vascular fibrous sheet in which there were only occasional shrunken cortical cells. In no instance was there any cortical regeneration. The process of destruction did not appear to be particularly active. Necrotic cells were seldom seen and lymphocytic infiltrations were not so dense nor so abundant as in the cases of Addison's disease here reported. However, small accumulations of lymphocytes were frequently found in those parts of the cortex in which destruction was most advanced. Larger collections of lymphocytes were scattered here and there in the medulla, but apart from the presence of these infiltrations, the medulla never showed any alteration from the normal.

The lesions in the adrenal glands in these cases differed in no essential respect from those found in the cases of Addison's disease, except in point of degree. Careful study and comparison of the microscopic sections left no doubt in our minds that the process of destruction was identical in the two series of cases. In the one instance the lesions had progressed to the point of producing adrenal insufficiency and death, while in the other cortical destruction was not so widespread nor advancing so rapidly that clinical signs and symptoms had appeared. The findings in these latter cases indicate clearly that the primary lesion is in the adrenal cortex, for in all of them the medulla appeared to be normal. It seems to be also the case that the zones of the cortex differ in their susceptibility to damage, the reticular zone being the

most liable to destruction and the glomerular zone the most resistant. Such a conclusion was suggested also by the study of the adrenals in the cases of Addison's disease. That these differences in susceptibility indicate differences, as yet unknown, in the function of the three zones of the cortex seems probable. No lymphocytic infiltrations could be found in the thyroid gland or kidneys in these four cases. This fact indicates that the infiltrations seen in these organs in the cases of Addison's disease were associated with the state of adrenal insufficiency rather than with the peculiar destructive process in the adrenal glands. The presence of similar infiltrations in cases of Addison's disease due to tuberculosis of the adrenals makes this quite evident.

Unfortunately, these cases of early adrenal damage offered no better clue to the etiology of the disease than did the more advanced ones. Nothing in their histories or in the associated lesions of other organs suggested a relationship which would point to a common etiological factor. However, a further study of such cases cannot but assist in the elucidation of the process and enhance our knowledge of this peculiar lesion of the adrenal gland.

SUMMARY

Five cases of Addison's disease, four of which had been treated with extracts of suprarenal cortex, are reported. All of them showed more or less complete "atrophy" of the adrenal cortex.

The destructive process in the adrenal glands consisted of a progressive necrosis of cortical cells with collapse of the stroma. In two cases there was regeneration of cortical tissue. The medulla was affected to a much lesser degree, usually showing only a slight increase in the density of the fibrous framework and some shrinkage of the medullary cells. Lymphocytic infiltrations were constantly present in the adrenal medulla and among the remnants of cortical tissue. Lymphocytic infiltrations in various situations constituted the most constant findings in association with the adrenal lesions. Marked hyperplasia of lymphoid tissue was not present in any of the cases. No lesions were found for which the treatment with extract of adrenal cortex could be held responsible.

The relation of the pathological findings to the clinical observations are discussed briefly. A consideration of the possible factors in the

etiology of the adrenal lesions leads to the conclusion that a circulating toxin of unknown origin and nature is probably the causative agent.

A brief account is given of observations upon four cases which showed the early stages of destruction of the adrenal cortex but which presented no clinical evidence of Addison's disease. The findings indicated that the adrenal lesion is primary in the cortex and that the three zones of the cortex differ in their susceptibility to damage.

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EXPLANATION OF ILLUSTRATIONS

(Magnifications of from 20 to 50 times have been used)

FIG. 1. A section of adrenal gland showing complete loss of the cortex except at the left end of the section where a few distorted cortical cells still persist. In this area there are numerous lymphocytes which obscure the individual cells. The medulla is intact and not greatly altered (Case 5).

FIG. 2. A section of adrenal gland in which destruction of the cortex is not quite complete. Scattered cortical cells, some of them necrotic, are still present between the strands of the collapsed stroma. There is a diffuse lymphocytic infiltration (Case 5).

FIG. 3. A section of adrenal gland showing complete loss of cortical and medullary cells. All that remains within the adrenal capsule is the collapsed framework of the parenchyma, infiltrated more or less densely by lymphocytes and a few large mononuclear cells (Case 4).

FIG. 4. A section of adrenal gland in which there is a total lack of cortical cells. The delicate fibrous framework is collapsed and contains a dense lymphocytic infiltration. A portion of the medulla is shown. The medullary cells are somewhat shrunken and toward the right side part of the medulla has undergone destruction (Case 4).

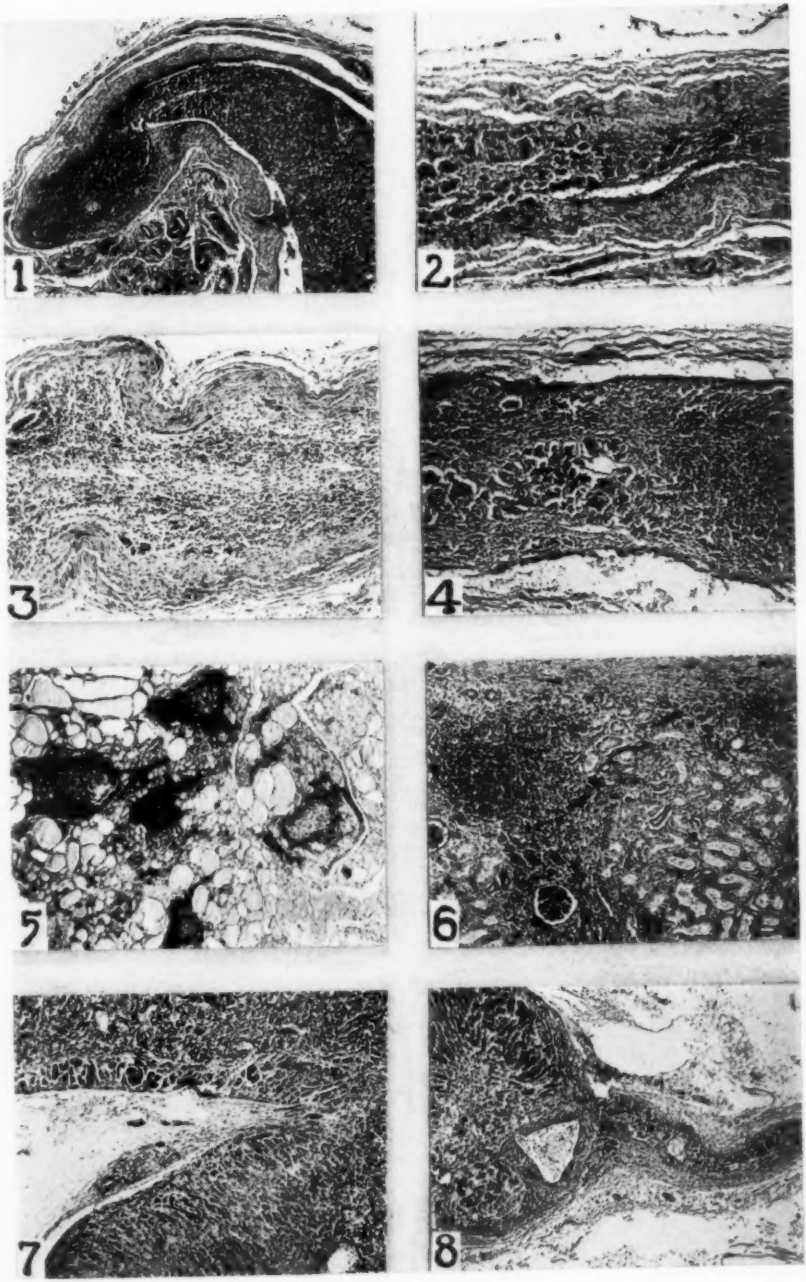
FIG. 5. A section of thyroid gland showing the dense interstitial accumulations of lymphocytes, some of which resembled lymphoid follicles (Case 2).

FIG. 6. A section of kidney in which two dense collections of lymphocytes may be seen just beneath the capsule. The tubules in their immediate neighborhood are shrunken, with low epithelium and thick basement membranes (Case 2).

FIG. 7. A section of the adrenal gland from a patient who did not have Addison's disease (No. 12557). Along the upper margin shown, the cortex has almost completely disappeared; it is represented only by deep-staining remnants of the zona glomerulosa. These are separated from the medulla by a thin layer of collapsed stroma. The medulla is normal. The cortex reaches its usual thickness along the margin of the gland shown below.

FIG. 8. A section of the adrenal gland from another patient who showed no clinical evidence of Addison's disease (No. 12318). At the right side the gland has been reduced to a thin fibrous sheet in which only a few small clumps of cortical cells remain interposed between the layers of the collapsed stroma. There is a moderate lymphocytic infiltration. This atrophied portion of the adrenal extended outward about four times the distance shown in the illustration.

(Micrographs by Mr. Milton Kougl.)



FIGS. 1–8

DEDICATION OF THE HENRY M. HURD MEMORIAL HALL, THE OSLER MEDICAL CLINIC AND THE HALSTED SURGICAL CLINIC

FRIDAY, OCTOBER 28, 1932

Dr. Joseph S. Ames and Judge Henry D. Harlan presiding

The following addresses were made:

HENRY M. HURD AT THE JOHNS HOPKINS HOSPITAL AND THE TRIBUTE TO HIM OF GEORGE K. McGAW

JUDGE HENRY D. HARLAN
President of the Board of Trustees

We have met today to formally dedicate to the purposes for which they were constructed three great buildings,—the Osler Medical Clinic, named in honor of William Osler, first Physician-in-Chief to the Johns Hopkins Hospital; the Halsted Surgical Clinic, named in honor of William S. Halsted, first Surgeon-in-Chief to the Johns Hopkins Hospital; and the Hurd Memorial Hall, erected in honor of Henry M. Hurd, the first Superintendent of the Johns Hopkins Hospital, a great Physician, a great Surgeon, a great Superintendent, worthy to be held in honor by all men, and especially by us in this place. Not alone their aid to humanity, their contribution to science in their respective spheres, but the service they rendered in establishing principles, methods, techniques, and a morale upon which the reputation of this Hospital so largely rests, entitles them to lasting remembrance. Their fame is our heritage, and we rejoice in the opportunity to connect their names with these three great buildings.

Others are to speak of Osler and Halsted. It is my privilege to say something in brief compass of Dr. Hurd's connection with this Institution, and of the friendship of George K. McGaw which led the latter, out of the generosity of his heart, to provide a fund which made possible the Hurd Memorial Hall in which we are assembled.

Dr. Hurd came to the Johns Hopkins Hospital in response to the

call of that early and wise Board of Trustees, most of whom were chosen by Johns Hopkins himself, on August 1, 1889. The Hospital had been opened the preceding May, and President Gilman had acted as its Director during the interval.

Dr. Hurd was peculiarly equipped to organize a new hospital, built by the Trustees after most careful consideration under the advice of Dr. J. S. Billings, upon a plan and with ideals that were then novel and striking. He had already organized and for eight years had administered with marked success a new hospital for the insane in the State of Michigan, and he found here a new opportunity to demonstrate still further his remarkable qualifications in hospital organization and administration, and to render notable service in promoting proper hospital care of the sick, particularly the indigent sick, and in advancing the standards of medical education and nursing. His task was no light one, and required ability of a high order. He was in accord with that group of forward-looking men who organized the Medical School of the University, that here was to be established a University School of a different order from any that existed in this country, where in addition to the better education of practitioners of medicine, the bounds of medical knowledge should be extended by encouraging research into the causes of disease with a view to its prevention as well as its cure. And he kept in mind the injunction contained in the Will of Johns Hopkins, the founder, that the Hospital should form a part of the Medical School for which he was providing by his will. It was not a little due to his statesmanship, his tact, his kindliness, his breadth of vision, his harmonizing influence, that there was created here among the staff of the Hospital and the University a spirit of coöperation and of generous appreciation and admiration, each for the achievements of the other, that has been a marked characteristic of the relations of the Hospital and the Medical School—a spirit that has attracted men to our service who otherwise would not have joined our staff, and who have shed great lustre upon the University and the Hospital.

When Dr. Hurd came here, he was in his 47th year, and in the maturity of his powers. Not a man of vigorous physical frame, he possessed an unbounded industry and a disciplined mind. His personality was engaging, and he was sagacious, tactful, capable of

keen sarcasm, which he occasionally employed; but essentially he was kind-hearted and generous. My acquaintance with him began six years later in 1895, when I was made a member of the Board of Trustees, still composed of some originally chosen. Of the Board as then constituted, I am, alas, the sole survivor. I cannot forget the kind interest with which Dr. Hurd showed me the Hospital, explained its departments, spoke of its ideals, and gave me information most helpful to a young and inexperienced Trustee. I think he felt it part of his duty to train new Trustees as he trained internes, but he did it delightfully. The relations he maintained with the Trustees were always cordial. He brought to them in the most orderly and intelligent manner the problems which they had to solve; he inspired their confidence in the wisdom of his recommendations; and deserved and won their support for the policies which he in his own way rather suggested than urged. For nearly twenty-two years Dr. Hurd performed with conspicuous ability and success the duties of Superintendent.

When in his 69th year, he felt that he should lay down the burden of work and responsibility which attaches to the office of Superintendent, the Trustees were not willing to lose the benefit of Dr. Hurd's knowledge, experience and wisdom, in the management of the foundation under their control, and plans were perfected to have him continue in the service of the Hospital as a salaried officer. He was made Secretary of the Hospital and a member of the Medical Board, in which positions, instead of exercising the power and authority of an administrator, he should have the functions and influence of an adviser. For 16 years until his death on July 18, 1927, he occupied these positions to the lasting benefit of this institution.

In addition to being Superintendent of the Hospital, Dr. Hurd was also the first Professor of Psychiatry. Indeed, it was in this field that he had won his early renown and a national reputation, and notwithstanding the exacting nature of his duties as Superintendent, he maintained his interest in the science of Psychiatry, and made rich contributions to its literature. He also found time to be Editor of the Johns Hopkins Hospital Reports and of the Hospital Bulletin, and he made these valuable publications. He was above all else a cultured, kindly, Christian gentleman.

Such was the remarkable man that George K. McGaw wished to honor. Mr. McGaw had become a Trustee in 1905. I think his name was suggested to the Trustees by Dr. Hurd. Both were prominent and faithful members of the First Presbyterian Church, and a warm friendship grew up between them. Mr. McGaw himself was a remarkable man. He came of good stock. His forebears were Scotch. He was born in Harford County. He was at the age of 17 a clerk in the Jacob Tome Bank at Port Deposit. He came to Baltimore as a young man and engaged in business, and by force of character and sagacity won for himself success, a not inconsiderable fortune, and became an important factor in the life of the City. He was public spirited, generous, warm-hearted, unaffectedly religious, a wise adviser, and a man of unusual business talent. He took a deep interest in the Johns Hopkins Hospital, and was a valued Trustee. In November, 1918, he addressed the following communication to the Board of Trustees:

"Gentlemen:

"I am handing you herewith 50 Western Maryland Railway 4% bonds of the par value of $50,000 and 300 shares of Baltimore and Ohio Railway 4% Preferred stock of par value of $30,000.

"In presenting to the Johns Hopkins Hospital these securities, I desire to accomplish two purposes which I have had for sometime in mind.

"First: It is my desire that the Western Maryland Railway bonds shall be the basis of an accumulating fund which may be increased by other additions and used for the construction on the grounds of the Hospital of a building to be named 'The Henry M. Hurd Building,' in honor of and in recognition of Dr. Hurd's services as Superintendent of the Hospital from 1889 to 1911.

"I suggest to the Trustees that such a building when erected shall be adapted for the following purposes:

"(1) To receive and care for the histories and records of the Hospital.

"(2) To receive and care for the books, paintings, pictures, etchings, photographs, etc., belonging to the Hospital.

"(3) To accommodate in a suitable hall or auditorium gatherings to promote philanthropic and religious work in connection with the Hospital.

"Second: It is my desire that the Baltimore & Ohio railroad stock shall constitute a memorial fund, which may also be increased by other additions, in memory of the Reverend Samuel A. Gayley, D.D. (my friend and teacher), Pastor of West Nottingham Presbyterian Church (from 1856 to 1903), and Principal of West Nottingham Academy.

"The income from this Gayley memorial will create at least a partial endowment

for the Henry M. Hurd Library Building, and I desire that the principal of the fund shall be preserved and reinvested from time to time in the discretion of the Trustees and the income only applied to the following purposes:

"(1) Towards the salary of a person or persons to care for the personal property in the Henry M. Hurd Library Building.

"(2) To promote philanthropic and religious work in connection with the Hospital, and while I mention religious work lastly, it is my wish that this feature of work be emphasized in order to fulfill the request of the founder of the Hospital, 'That the influences of religion should be felt in and impressed upon the whole management of the Hospital,' undisturbed nevertheless, 'by sectarian influence, discipline or control.'"

Respectfully yours,
(signed) George K. McGaw."

The gift was gladly accepted. In July, 1919, he increased the fund for the Hurd Building by an additional gift of 200 shares of Pennsylvania Water & Power Company stock, having a market value of $17,500.

Mr. McGaw did not live to see the accumulating fund which he established grow to an amount sufficient to erect a worthy building. He died on September 9, 1919. Illustrative of the warmth of the friendship which existed between these two men, I quote part of a letter which Dr. Hurd wrote to Dr. Cullen in reply to a telegram informing Dr. Hurd of Mr. McGaw's death—"I have been greatly shocked by the unexpected death of the best of friends, and I know of no one who may occupy the vacant place in quite the same way. He was so noble in his plans, and so modest in carrying them out, so that his own work might be minimized. I always felt him to be a rare man. We, all of us, ought to be better men for having known him. I have written Mrs. McGaw, but I felt that I could not in any way tell her properly how I loved him." The souls of these two men were knit together as the soul of Jonathan was knit to the soul of David. Twelve years passed, and meantime the fund for the Hurd Building grew by accumulation of interest until it seemed adequate to carry out the intention of the donor. The Welch Memorial Library had provided adequately for the first and second of the purposes for which Mr. McGaw had suggested that the fund might be used. The third was open and when plans were in preparation for the new Medical and Surgical Clinics, one to be named for Osler and one for

Halsted, opportunity came to place between these buildings a much needed auditorium which should be sufficiently monumental, dignified and useful to fulfill Mr. McGaw's wish, and bear the name of Henry M. Hurd. The success with which what was conceived has been accomplished is due to the skill of the architects, Messrs. Sperry, Edmonds and Crisp, in association with Mr. Lawrence Fowler, and to the interest and advice of Dr. Smith and Trustees Randall and Jacobs.

This building, ladies and gentlemen, is a tribute of love and friendship,—the tribute of George K. McGaw to his friend, Dr. Henry M. Hurd, and we here dedicate it to the noble uses for which it is intended.

DR. HENRY M. HURD—HIS INFLUENCE IN HOSPITAL ADMINISTRATION

DR. WINFORD H. SMITH

Director of the Johns Hopkins Hospital

It is difficult for many of us to realize what the status of Hospital Administration was at the time when Dr. Hurd came to The Johns Hopkins Hospital. We are accustomed to think of hospitals as we now find them, or as we have known them in recent years. Forty-three years ago these institutions were quite different. At that time, hospitals were looked upon more as a refuge for the poor, rather than as desirable or needed for any other class of society. The development that was to transform our hospitals into institutions with accommodations for patients from all economic levels had started, but was not yet well under way.

Those in charge of these institutions were for the most part poorly trained for such work, and all too frequently were entirely unsuited for the task. Most hospital superintendents of that day were nurses or ministers, or men of some business experience, such as stewards, or storekeepers. Some were physicians who still attempted to practice medicine and gave only part of their time to hospital administration, which they found desirable, because the demands upon them for private practice were not sufficient to occupy their time or to provide a living. To be sure there were exceptions, and most of these were physicians who had a background of experience similar to that of Dr. Hurd. The leaders in the development of better hospital administra-

tion, more intelligent planning, and better hospitals conceived and operated along the lines of broader service, were largely to be found in this latter group.

Dr. Hurd became one of this group; and their names are written large in the history of the development of hospitals in this country. They were Dr. Hurd, Dr. C. Irving Fisher at the Presbyterian Hospital, New York; Dr. George H. M. Rowe at the Boston City Hospital, Dr. Herbert Howard at the Massachusetts General Hospital, Dr. John M. Peters at The Rhode Island Hospital, and a few others. Dr. Peters is the only one now living.

These few medical executives had a great influence upon the development of hospitals and hospital administration. They played an important part in founding the organization now known as The American Hospital Association, the membership of which represents some two thousand of the hospitals of this country and Canada.

Dr. Hurd was an active and respected member of this group. Like most of them, he undertook the administration of a general hospital after several years of experience in hospitals for the insane. At that time these hospitals offered about the best experience to be obtained by way of fitting a man for a career in Hospital Administration. Dr. Hurd had, as preparation for his task at Johns Hopkins, eight years as assistant physician and assistant superintendent at the Michigan Asylum for the Insane, and eleven years as Medical Superintendent of the Eastern Michigan Asylum at Pontiac. From this post he came to Baltimore. In addition, he had previously studied hospital work in New York and had engaged in private practice and dispensary work in Chicago.

In taking up his work at Johns Hopkins he was entering a new field, but one for which he was probably as well prepared as anyone available at that time. He could not have realized how important this new work was to be. He came to administer not only a general hospital, but a hospital which was to set an example as a teaching hospital closely associated with a medical school, and both of which, in cooperation, were destined to play a most important part in the development of medical education.

To be sure, he was most fortunate in that he was associated with that remarkable group of men—Welch, Osler, Halsted, and Kelly—

as well as their younger associates, who were also unique in many respects and who have nearly all achieved distinction. But the record of his accomplishment at Johns Hopkins would have been quite different had he not had the educational background, the personality, and the intelligence which enabled him not only to take his proper place in this environment, but also to appreciate in full measure the opportunity, and to contribute his share to the development of this Hospital as a teaching hospital, a centre of research and of medical education.

In this connection, it may be said, that under the guidance of this original staff, The Johns Hopkins Hospital quickly became the outstanding example in this respect. This was really the first hospital to devote itself intensively to the aims of medical research and medical education. To Dr. Hurd should go a full measure of credit for the part which he played in this new departure. Had he not been able to appreciate the advantages to the hospital, as well as to the school and to medical education, he might have seriously interfered with the development which took form. He entered whole-heartedly into the movement and contributed his full share to the encouragement of that splendid spirit of coöperation and that atmosphere free from quarrels and bickerings, which has ever been one of the outstanding features of this Institution.

Probably his influence in hospital administration was most pronounced in this respect. He was looked upon as the leading authority on the problems of the teaching hospital and he undoubtedly exerted great influence in extending the use of hospitals for teaching purposes, which has now become so general. It is doubtful if he could have contributed as much in any other way.

In one other respect he became an outstanding figure in the hospital world, and that was in his attitude toward Nursing Education. While his previous experience had given him little opportunity to consider the problems of undergraduate schools of nursing, of which there were few at that time, nevertheless he quickly sensed the importance of this movement and at once took a stand with the leaders of nursing education in working for higher standards for admission, for higher standards of education, and more thorough training. In recent years, many have advocated the endowment of schools of nursing.

As long ago as twenty-six years, Dr. Hurd gave an address at Lakeside Hospital entitled "Shall Training Schools for Nurses be Endowed?" in which he maintained that they should be endowed.

Throughout his life, after coming to this institution, he constantly supported the movement for better standards in everything related to nursing education. It is often difficult to evaluate the influence of any one individual upon the various movements and events of his time. Dr. Hurd was not of the aggressive type. He was quiet, frail in appearance, and rather retiring in his manner. His influence was exerted more by his example as a man, as an expert in his field, and by his kindliness, which led him to be consulted frequently.

A colleague has said of him: "You feel instinctively that you had to do with one who knew no guile or self-seeking, but who appreciated it to be his duty to place his powers of mind and heart unreservedly at the disposal of his associates or his fellow men."

After coming to The Johns Hopkins Hospital, one finds in the long list of his addresses and papers, discussion of the following subjects:

The Relation of the General Hospital to the Medical Profession
The Relation of Hospitals to Medical Education
Laboratories and Hospital Work
The Medical Service of Hospitals
Hospitals, Dispensaries, and Nursing
Hospital Construction from a Medical Standpoint
The Educated Nurse and Her Future Work
The Medical Organization of General Hospitals
Shall Training Schools for Nurses be Endowed
The Proper Length of the Period of Training for Nurses
State Registration for Nurses
Co-operation Among Hospitals
Florence Nightingale—A Force in Medicine
The Proper Relation of the Superintendent to the Trustees of a Hospital
The Proper Division of the Services of a Hospital
The Hospital as a Factor in Modern Society
Hospitals and the Reform in Medical Education

The list could be extended greatly, but these topics indicate the chief lines of his interest. It was along these that he made his influence felt in hospital administration.

Dr. Hurd always retained his interest in Psychiatry and his con-

tributions in that field were of great value. That phase of his life is outside my knowledge. I speak of him only in his relation to the general hospital field.

If I may, I would like to say just a few words of a more personal nature. Dr. Hurd was the first superintendent of this Hospital and held that post for twenty-two years. As his successor, I am now in my twenty-second year. Therefore, I have had abundant time in which to learn what others thought of him and I can truly say that I have never heard anyone speak ill of him. Times without number older members of the Staff and former House Officers have told me of their great affection for Dr. Hurd and of the many acts of personal kindness and consideration shown by him to them and to others connected with the Hospital.

I would like to quote from a letter received from Dr. Hurd in which he extended to me an invitation to come here to be interviewed by the Board of Trustees.

"I had not written to you before because I was anxious not to seem to dictate to the Trustees who should succeed me. I write now to ask you to come down to see a Committee of the Board and to look over the situation. I hope with all my heart that you can come to take charge of the Hospital."

I never had occasion to doubt the sincerity of his words.

Dr. Hurd remained as Secretary of the Board of Trustees for sixteen years after I came here. He sat with the Board at its regular meetings, at which time it was my business to report on the work of the Hospital and to make recommendations. There must have been many times when he disagreed heartily with me, yet never once in those sixteen years did he, by word or act, in any way embarrass me in my work, quite the contrary in fact. To me that is a remarkable record. Few men could lay down their work after twenty-two years, and although in continuous contact with a successor, refrain from doing anything or saying anything to cause embarrassment.

It would be impossible for me to express my feelings for Dr. Hurd and all that he meant to me.

I am glad that we have this splendid memorial erected in his honor. It seems to me that no form of memorial could have been more appropriate. In this hall, bearing his name, are held the meetings of

The Johns Hopkins Medical Societies, and meetings of nurses and nursing organizations. Here teaching is carried on and here are held the numerous other gatherings identified with the life of the Hospital. These activities, aside from his routine duties, were the real life and interest of Dr. Hurd at The Johns Hopkins Hospital.

In conclusion, may I take a moment to read extracts from letters received from a group of Dr. Hurd's intimate associates and friends:

Dr. Thomas Howell, Superintendent of New York Hospital: "Dr. Hurd was an inspiration to hospital administrators. We regarded him as an ideal hospital superintendent. He was always willing to advise and help and thus endeared himself, especially to the younger men. His writings were most valuable contributions to hospital literature. We all learned from them.

"It is a matter of deep gratification to me, and I am sure to all other hospital superintendents, that the Henry M. Hurd Memorial has been erected in Dr. Hurd's memory."

Dr. W. L. Babcock, Director, Grace Hospital, Detroit: "It is a matter of great regret that I cannot be present. Dr. Henry M. Hurd was always a mentor to me. He was my preceptor while I was a medical student in Baltimore. His advice and assistance to myself and the younger group of hospital administrators throughout his long and successful hospital administration have been reflected in the progress of hospitalization throughout the entire nation.

"It is fitting that such a memorial as you dedicate today be perpetuated as a memorial and reminder of a great hospital administrator."

Dr. Joseph B. Howland, Superintendent, Peter Bent Brigham Hospital: "I am sorry I shall be unable to be present.

"It was a fine thought, perpetuating Dr. Hurd's name in connection with a hall largely to be used for educational purposes. Dr. Hurd, ever a 'bookish' man, and a precise teacher, would, I am sure, have taken great pride in feeling that his name was connected with a room set apart for teaching."

Dr. John M. Peters, Superintendent, Rhode Island Hosp.: "It is gratifying to Dr. Hurd's many friends to know that such a memorial has been erected in his honor, and I do not know of a more fitting one than that which can be used to such practical purposes in the future.

"I met Dr. Hurd a short time after the opening of the Johns Hopkins Hospital, and was in friendly touch with him during his whole connection with the institution. As one of the younger men entering into hospital administration work at that time, I appreciated especially his kindness and his willingness to advise on the problems presented to him.

"His interest and enthusiasm, his kindness and willingness to advise others, never waned."

Dr. Frederic A. Washburn, Director, Massachusetts General Hospital: "I am very much pleased that so fine a memorial to Dr. Hurd and his memory has been erected. He was one of the leaders in hospital administrative work when I was a young man. I shall always remember with gratitude the kindly, sympathetic interest which he took in the young men just beginning their careers in hospital administration. He was prominent in a small group of men who twenty-five years ago were striving to place hospital administration upon the high level which it has since attained. His nature was so modest that he little realized what an inspiration he was to younger men."

Dr. S. S. Goldwater, for many years Director of Sinai Hospital, New York: "The dedication of the Henry M. Hurd Memorial Hall is a gratifying tribute to the life and services of an eminent member of the medical profession, distinguished for his whole-hearted devotion to the Johns Hopkins Hospital and to the advancement of hospital service generally.

"Among hospital administrators, Dr. Hurd was looked up to as a leader and teacher; his experience, his knowledge, and his judgment were a reservoir upon which those who needed guidance in dealing with difficult hospital problems were always welcome to draw.

"To any public discussion in which Dr. Hurd participated he gave a note of distinction and of moral elevation. His kindness endeared him to many. I am delighted at the honor which is being done to his memory."

Miss Adelaide Nutting: "To work in constant association with Dr. Hurd, as was my privilege for a number of years, was a most interesting and stimulating experience. I look back upon it as a liberal education. Among the unforgettable things of those days are the memories of

the wisdom and resourcefulness which he would bring to bear upon some of these extraordinarily difficult situations which can arise at almost any moment in the complex life of a great hospital; of the clarifying light he could throw upon a tangled administrative problem, to which there had seemed to be no solution ever possible. I remember his caustic wit, his keen shrewd criticism, his penetrating judgments of people and their actions.

"But most of all do I recall how sympathetic he was, how kind and patient and truly helpful to those who went to him in real trouble and perplexity. Perhaps some of the pleasantest memories of life in the hospital might be found among those infrequent moments when with the endless, worrying details of the day's work temporarily disposed of, Dr. Hurd's talk would slip into other channels, and from the rich resources of his scholarly and sensitive mind, there would be drawn apparently inexhaustible stores of information, reminiscence and anecdote. There are a good many of his friends who can doubtless remember such moments, with similar appreciation.

"I hear the memorial is very beautiful and it seems to me to commemorate in a fitting way certain aspects of Dr. Hurd's life, which made him so familiar a presence at those gatherings, of staff and students, friends and associates, which are so constant a part of the tide of life that flows through a great teaching hospital."

PRESENTATION OF BAS RELIEF

WILLIAM R. DUNTON, JR., M.D.

Instructor in Psychiatry

For a number of years the friends of Dr. Henry Mills Hurd have felt that the portrait which hangs in the lobby outside this hall did not do the subject justice, that however excellent it might be as a painting it did not convey anything of his delightful personality. Therefore, in February, 1930, a committee was formed under the leadership of Dr. Edward N. Brush to secure a more fitting memorial. This committee decided to place a bronze bas-relief in this hospital and a portrait in Osler Hall. In this it had the approval and coöperation of Dr. Hurd's daughters. The response to its appeal was so generous and so widespread that both objects have been attained.

The portrait by Mr. Thomas C. Corner was presented to the Medical and Chirurgical Faculty on April 27th, 1932, by Dr. Edward N. Brush. Today we meet for the formal exercises attending the dedication of this building including the presentation of the bas-relief so that the plans of the committee have been consummated.

During the Summer of 1893 I had the privilege of serving as a substitute interne on the staff of Dr. Howard A. Kelly. During my sojourn here I heard frequent references to one "Hank," whom I learned was Superintendent of the hospital, then absent on a vacation. The following Spring I was invited to attend the Resident's Dinner and the morning after stopped at Dr. Hurd's office to pay my respects and thank him for his hospitality. I had somehow gained the impression that Dr. Hurd was a stern, reserved man and was pleased to find him a genial, kindly gentleman. Coming to Maryland two years later brought frequent contacts with Dr. Hurd, and during the years there developed a strong bond of friendship between his family and my own. Early in this period I learned much of Dr. Hurd's past labors, of his reputation as an eminent psychiatrist, and his splendid record as a hospital administrator in Michigan. This record was so good that Dr. Richard Gundry had recommended him to Mr. Frances White, then President of the Board of Trustees of this hospital, as best qualified to launch it on its active career. A glance at Dr. Hurd's bibliography is sufficiently convincing of his earnest efforts to advance psychiatry, and a perusal of his papers discloses his admirable literary style as well as his forceful writing. At medical meetings his discussions showed clear thinking, wide study, and sound common sense.

It should be remembered that Dr. Hurd served as secretary of the American Medico-Psychological Association from 1893 to 1897, later being Vice-president and President, and that it was his guiding hand which developed that organization. He was also chief editor of the American Journal of Insanity and afterwards editor *emeritus* until he resigned. I am sure that others who have assisted Dr. Hurd in his editorial duties feel with me that such contacts were to our advantage.

This brief mention of a few of Dr. Hurd's activities which are perhaps not so well known as his achievements in developing this hospital and editing its periodicals are but additional evidence of what a

great man he was, yet I like best to think of him as a friend who encouraged many in their labors, who was a comforter in time of trouble, and through it all showed such kindliness. His piquant humor saved his few scoldings from leaving any sting. As one who regarded Dr. Hurd as a lovable friend and mentor I feel honored in being chosen on behalf of about one hundred donors to present the bronze bas-relief by Mrs. Simone Boas which is on the wall of the adjoining room.

THE OSLER CLINIC

WILLIAM S. THAYER

It is over three and forty years since Osler opened the medical clinic. It was a small clinic then. There were two private wards, i.e., B, now buried in the Wilmer clinic, gynecological, and C, of two floors, medical and surgical. There was one surgical ward, D, and one medical ward, F. Wards E and G were divided between medical and surgical services, and H was a gynecological ward. There was a large isolating pavilion, I. There was no special building for coloured patients who were cared for in the back rooms of the old long wards. There was no obstetrical service. The pathological laboratory was a small, two-story building. The medical school was, as yet, a dream, but a goodly number of post-graduate students followed the visits in the wards and worked in the pathological laboratory. The senior staff consisted of Welch, Osler, Halsted and Kelly, to which Hurd, the wise and kindly director, and Councilman, the beloved resident pathologist, should be added.

The objects and ideals of the institution were the same as those of today. But the basis of our knowledge and our means and implements of study, were very simple, as one looks back upon them. Bacteriology, a relatively new science, was giving to us our first intelligent understanding of infectious disease. Our conception of the principles of immunity was in its infancy. The Italians were beginning to separate Laveran's haematozoa into species. Osler had always been interested in parasitology, and had quickly grasped the significance of Laveran's discovery, and much of our time in the early years was given to the study of the malarial parasites and other protozoa, notably Amoeba coli.

The laboratory procedures in the medical service and in the hospital at large consisted of cytological examinations of the blood and simple chemical and cytological examinations of excreta, exudates and transudates. Outside of the department of pathology there existed but one laboratory, a small room under ward G, used by the house officers of all services, and graced by the name "clinical laboratory." To this no regular attendant was attached, and it was usually in an inconceivable state of disorder. No chemical work deserving the name was done in the hospital; no quantitative work beyond crude estimations of urea and of sugar. In this we were distinctly behind some other contemporaneous American clinics.

In two respects, however, the medical clinic stood out in contrast to others, in its organization and in the universal use of the microscope by the bedside notably in the examinations of fresh specimens of blood.

In the beautiful, large, fresh wards—for those wards were a luxury which anyone who knew them will always regret—with their famous ventilating system, rarely put into correct practice but so good, fundamentally, that the air was almost always pure, whose windows were so large that it was generally beyond the physical power of a nurse to open or close them or their heavy blinds—in those big, fresh wards the patients were well studied by the house officers and post-graduate students by the simple methods which were ours, under the direction of a great and inspiring master. Osler showed good judgement in the selection of his internes, considering not only their medical attainments but their human and social characteristics.

From the outset he planned a senior medical staff, a resident and one or more assistant resident physicians. He desired that the "Resident Physician" should come to occupy much the same position as that of the first assistant in a German clinic. In this fashion he hoped to attract to his department men who might desire to spend a considerable number of years in study and teaching, who might even do a limited consulting practice, stepping eventually from this position to the professorial chair at another institution. One of his resident physicians spent seven years at his post, having become Professor of Clinical Medicine in the University before leaving the hospital.

Osler was essentially a naturalist. He was an experienced pathologist in every sense of the word and he was a master of the fundamental

procedures of physical examination. He was an able diagnostician and his keen powers of observation with his remarkable human sympathy, gave him an unusual understanding and foresight in prognosis.

But Osler was not only an able pathologist and physician, he was a very wise therapeutist. Few "specific" measures of prophylaxis and treatment were then at our service. In the employment of such simple measures of treatment as were proven to be of value, in the intelligent use of rest and massage and other physical methods, especially in the all important treatment of the patient from the mental and human standpoint, Osler was an admirable therapeutist who taught us truths of inestimable value, forgotten sometimes today by those whose therapeutic store is so much richer.

But looking back on those days one realizes on how meagre a basis of fundamental knowledge we were obliged to act.

At the outset the medical service had not yet learned the possibilities of surgery, but a master, in his tiny operating room with the old wooden table, was demonstrating to us the possiblities of a thorough aseptic procedure and exemplifying the laws of careful, conservative surgery, while Dr. Kelly was performing prodigies of technical skill, and, soon, the close and informal relation between medical and surgical staffs taught us what we might expect of the surgeon with early and cordial coöperation. I well remember the first patient that I referred to Halsted for an appendectomy between attacks, and the extreme caution with which the operation was approached. Only a year ago the patient, a distinguished man of science, told me that just before etherization the conscientious "Professor" came to his bedside and told him that he had time yet to change his mind. Soon the much needed coloured wards were built, materially enlarging the clinic.

With the opening of the medical school, so eagerly awaited by Osler, came new life in the advent of Mall, Howell and Abel. By their wise example and precept the university spirit was greatly intensified and their admirable laboratories became centres from which student and clinician alike gained help and inspiration. In 1896 we found ourselves finally with clinical clerks in the wards, the greatest and most life-saving blessing that a hospital could crave, one of the most precious contributions of Osler to American medicine. These were the days of typhoid fever, the victims of which occupied more

than half of the service for several months of the year. Student assistants gave us for the first time the power to make the necessarily frequent examinations of blood, to follow the patient from hour to hour, and to detect in time the perforation or the grave haemorrhage. These student assistants have saved many lives.

The school grew rapidly. Roentgenology contributed its miracles to the diagnostic art and, in Baetjer, added to the staff a fine, much loved and most stimulating figure. Our knowledge of the infections increased apace.

The loss of the Chief was a heavy although expected blow, but, with Barker, came the development of the first adequate bacteriological, chemical and physical laboratories in the medical department, a great contribution which should never be forgotten. The Phipps, the Harriet Lane and the Brady clinics were erected.

In 1914 the Welch fund enabled us to reach out farther toward our ideals and place our clinical departments on a basis better adapted to the needs of the university, and Janeway brought to the medical service his exceptional abilities, his ripe experience, his high ideals. His untimely death deprived us of the ablest American clinician of his generation and of one of the most beautiful characters that I have known.

Janeway and his immediate successors were labouring with a department of small and disconnected units, spread over a large area, insufficient in beds and in laboratory space, difficult to administer. Gradually improvements came; the new pathological laboratory, the woman's clinic, the dispensary and laboratory building and, at last, the fine medical and surgical units and the amphitheatre which perpetuate the names of Osler, Halsted and Hurd, the structures which we dedicate today. On such an occasion as this, when one naturally looks back longingly and lovingly to the masters of yesterday, it is really startling to compare the crudities of those days with the opportunities which are ours today. Forty-three years ago, two wards, the tiny, so-called laboratory, and a staff of five, the Chief and four house officers. Today the beautiful clinic with all its laboratories and opportunities for study, its staff of residents, fellows and voluntary assistants in addition to the many secretaries and laboratory assistants, forty-seven in all, exclusive of the out-patient department;

staff and students, with a basic knowledge of the natural sciences so far beyond that which was ours but a few years ago, investigating questions involving the physiology and pathology of function and therapeutic action by scientific quantitative methods. Our diagnostic procedures are much more accurate. Our knowledge of the physiology of function has greatly broadened our conceptions of the nature and significance of symptom and disease. How many more or less specific methods of prevention and treatment have been added to the armamentarium of the student and practitioner of medicine! Forty-three years ago our diagnostic methods, depending largely on the skill and intelligence of the physician, were relatively simple. Today, while it is not one whit less important to be a good observer and to possess common sense and powers of reasoning, while skill in the use of the simpler methods of physical exploration is as necessary as ever, how many other aids have we in the practice of medicine! If forty-three years ago the pharmacopeia drawn upon in Osler's wards was relatively small, so much so that, by the popular polypharmacists of the day, we were criticized as therapeutic nihilists, how much fruitful scientific work today is given in chemical and pharmacological laboratories, to the building up, on sound principles, of substances which are used therapeutically no longer at random but on a sound physiological basis. I like to think that time has testified largely to the wisdom of our great predecessor in using, so far as possible, only those measures of treatment of which the action was understood, from which the dangers were eliminated.

Would that the Chief might be here today to see the work of his worthy successor and his staff! He should have been, for his was the best example of perfect living that I have known. He would have been but eighty-three years of age which should have been youth for him. How happy he would have been to see the fulfillment of so much that he had desired.

And the future? What will another forty years bring? Who can tell?

This much we know: it is for us to prepare the future. It is on us that the future will depend. Osler implanted in this department a spirit of enthusiasm, of simplicity, of good fellowship, of coöperation, that is not likely soon to disappear. He established a clinic in which

everyone who had a proper basis and the real thirst for knowledge could work. He who accomplished something was recognized, and received credit for his accomplishment. Of this clinic it could not be said that the work of student or assistant was appropriated by the Chief.

Osler impressed upon his students the duty of recognizing and giving credit to the work of others at home and abroad. He welcomed the visitor and he urged his associates to travel and to enter into relations with those of other provinces and other countries. He loved to call himself a peripatetic. Osler established a clinic in which the human relations were open and simple; in which formality and jealousy were unknown. His spirit reached all who worked under him. That spirit lives in Longcope's clinic today as it did in the beginning, and if that spirit persists we may be sure that the future will be worthy of the past.

Who can tell? It may be that forty years hence our grandchildren will look up to the names of some of the modest workers of today with the same reverence and affection with which we regard the names of Osler and Halsted and Hurd.

THE HALSTED SURGICAL CLINIC

JOHN M. T. FINNEY

This occasion, one of the main objects of which is to do honor to the memory of three of those intimately associated with the earliest beginnings of the Johns Hopkins Hospital, cannot fail to recall to the minds of many of those present a flood of memories centred about these and other distinguished personages, some of whom are happily still with us, whose names are known and honored not alone locally, but are world-wide, and whose fame has to do with events closely connected with this Hospital, some of which were epoch-making, not only in its history but also in the history of scientific medicine.

Undoubtedly, the thought uppermost in the mind of everyone present here today is one of thankfulness and appreciation of the generosity of those whose munificent benefactions have made possible these beautiful and much needed additions to the already imposing plant of the Johns Hopkins Hospital. To each one of these new units has

been attached the name of one who has helped materially to make this Hospital what it is today, an outstanding centre of scientific medicine, known and respected as such throughout the civilized world. Henceforth, there will have been permanently incorporated in the Hospital group memorials to four of those most prominently connected with its earliest beginnings,—Dr. Welch in the Library, Drs. Osler and Halsted in the Medical and Surgical Clinics, respectively, and Dr. Hurd in this beautiful Assembly Hall, in which we are now gathered. It remains for some appropriate foundation to be established to perpetuate the name and fame of that other illustrious member of the "Big Four," who, conjointly with those whose names have just been mentioned, has brought fame and reputation to this Hospital, and by the brilliance and versatility of his genius, and the originality of his methods, has not only greatly advanced his chosen surgical specialty of gynaecology, but has also contributed not a little to the science and art of surgery in general. I refer, of course, to Dr. Howard A. Kelly. In this connection, it would be fitting also to remember by suitable memorials, the names of Dr. John S. Billings and Dr. J. Whitridge Williams, the former who did such extraordinary work in the planning and organization of the Hospital, and the early establishment of its Library, and the latter for his valuable contributions to, and his leadership in, his chosen field of obstetrics. This recital by no means exhausts the list of names of those worthy to be permanently memorialized by the Hospital, but more extended mention of them at this time would lead us too far afield. It remains for those who come after to maintain the ideals and to advance still further the traditional high standards thus early established, and so make of this Institution a fountain of knowledge from which shall flow a never-ending stream of beneficent influences for the healing of the Nations.

Would that someone who was privileged to participate in and enjoy the delightful experiences attendant upon life in this Hospital in its early period, and who has the gift to paint a word picture of those halcyon days, would do so before it is too late. It would require a real artist to do them justice, for nothing could have been more delightful than the spirit of good fellowship that existed everywhere. We were one large family, each interested in the other's problems and

anxious to aid in every way in their solution. The atmosphere that pervaded the entire Institution was altogether charming; intellectually stimulating, and at the same time delightfully informal. Led by Dr. Welch, the chiefs of departments and the extraordinary group of younger men that they had gathered about them were, of course, responsible for this unique state of affairs. Nothing like it had existed previously, and it is doubtful if, in view of ever changing conditions, its like will ever be seen again. The time was ripe and the stage was set for progress in the medical sciences, and by a fortunate combination of circumstances the occasion and the men met here in the Johns Hopkins with the happiest results.

As one of the original, but, alas, gradually dwindling group of charter members of the Hospital Staff, it is perhaps fitting that I should devote the remainder of the brief time allotted to me, to a necessarily very sketchy review of the development of the Department of Surgery in the Hospital, under the leadership of that Master-Surgeon, William Stewart Halsted.

Some years before the formal opening of the Hospital, on May 7, 1889, Dr. Welch had gathered about him in his laboratory a group of earnest students, eager to be initiated into the mysteries of modern scientific medicine as it had been developed in the leading European clinics and laboratories. This group formed the nucleus of the Johns Hopkins School of Medicine. Under the inspiring leadership of our beloved Dr. Welch, then as now, *facile princeps*, the outstanding figure in scientific medicine in America, whom every medical gathering delights to honor, especially a gathering of Hopkins men and women, the Johns Hopkins Hospital and Medical School have gradually developed into what they are today. Prominent among these disciples of Dr. Welch was Dr. Halsted, who also had enjoyed the advantages of an extended period of European study. Even before coming to Baltimore from New York, Dr. Halsted had established a reputation as a surgeon and scientific investigator of more than ordinary ability. He had already begun that remarkable series of valuable contributions to the science and art of surgery, to be thereafter continued uninterruptedly, throughout his entire career, which have made humanity his debtor, and his name and that of the Johns Hopkins Hospital known and honored wherever scientific surgery is practised.

Dr. Halsted has left the imprint of his personality and scientific genius not only upon the surgery of this Hospital, but through his many valuable contributions to existing knowledge, his published works, and the many surgeons trained by him, some of whom are now filling with distinction chairs of surgery in some of our leading universities, has profoundly influenced the surgical thought and action of his time.

As one looks back over the early days of the Hospital and compares conditions as they were then, with those which now obtain in the up-to-date Halsted Surgical Clinic; the makeshift operating-room with its wooden operating table, the primitive character of its entire arrangement and equipment with everything pretty much afloat, due to the sloshing around of the various antiseptic solutions used in irrigating the wounds, and disinfecting the floors and walls, one cannot but marvel at the character and amount of surgery then done, and the excellent results obtained. This phenomenon, for such it was, can only be explained by the insistence by Dr. Halsted upon the meticulous observance, by his Staff and by himself, of certain fundamental principles underlying infection and wound healing, namely, the absolute control of contact and rigid antisepsis as then practised (asepsis was a later development); the utmost care and gentleness in the handling of tisses; perfect haemostasis; the avoidance of unnecessary strangulation of tissues by too tight ligatures or sutures; careful apposition of wound edges; the omission of the indiscriminate use of drainage tubes; the avoidance of too tight dressings and bandages, and the provision of physiological rest for the affected part. As the knowledge concerning the causes of infection of wounds and the methods of prevention increased, dependence came to be placed more and more upon assisting in every way the *vis medicatrix naturae*, and less and less upon chemical antiseptics, valuable as Lister's pioneer work had proven them to be. Thus gradually antisepsis was superseded by asepsis, and heat as a germicide in the operating-room largely replaced chemicals. Dr. Halsted early introduced the use of the rubber gloves, one of the greatest single contributions to the operating-room technique ever made. Just here enters a touch of Hospital romance. The use of rubber gloves in the operating-room was first suggested in order to protect the hands of the then operating-room nurse, the

future Mrs. Halsted. And so it came about, that here in the original makeshift operating-room, poorly adapted for its purposes, under apparently most unfavorable physical surroundings, was evolved, step by step, and put into daily practice, the most perfect aseptic technique, it may be safely said, that could be found anywhere at that time, and surgical results were being constantly achieved that challenged comparison with those of any other clinic in this country or abroad.

Listen to the impression made upon one observer well qualified to judge, by the character of the work done in Halsted's Clinic in the earlier days of the Hospital. He writes,—"I had come to Baltimore looking forward especially to the privilege of working near Welch; secondarily, to the pleasure of being with Osler. I knew little about Halsted or Kelly. Coming from a hospital which rejoiced in a surgical tradition second to none in the United States, I had been familiar with good surgery, but the technique was far from being what it is today. Abdominal surgery was in its infancy. During my internship, I had never seen the abdomen opened freely, save in an occasional operation for a pelvic tumor. In appendicitis one waited invariably for the formation of an abscess. In the middle of October, 1890, I arrived in Baltimore. Inside of twenty-four hours, I found myself in an atmosphere where the certainty of post-operative results was assured as it is today in the best clinics; where the abdomen or the knee joint was explored with impunity. In Halsted's little operating-room, with the old wooden table, the antiseptic technique was so perfect that there was never a moment of anxiety. I could not believe my eyes. It was like stepping into a new world. At this time Halsted's technique was unique, and the sureness and perfection of his results seemed to me then and seem to me now the nearest thing to a miracle that it has been given to me to witness."

To a Johns Hopkins audience, it will be unnecessary, I feel sure, to give the name of the author of this quotation, so characteristic are the style and diction, so I will leave it to you to supply it.

It is a curious fact that the Johns Hopkins Hospital occupied for years the anomalous position of a large general hospital, carrying on an active surgical service, without the facilities offered by an ordinary, not to say modern, operating-room suite. The reason for this astonishing fact was that at the time the plans for the Hospital were

drawn, surgery was in such a transition stage that Dr. Billings, the architect, very wisely decided to leave to the surgeon to be appointed the planning of his own operating-room.

When Dr. Halsted took charge in 1889, surgical technique was still in its infancy. In fact, it was in such an unsettled state that Dr. Halsted himself waited until he could formulate his plans with more certainty. Meanwhile, first one makeshift and then another were tried, until finally a plan was decided upon, and a very modest operating suite constructed. For some years, the main operating-room was located where the accident room now stands. Then it was moved into the basement under Ward G, where it remained for quite a long while. Next, what were then considered to be palatial quarters were constructed on the top floor of the building, now used for teaching purposes by the Nurses Training School. Finally, the present commodious quarters were erected and have since been occupied.

Now comes this splendid Halsted Clinic, and it may at last be said that physically, at least, the Department of Surgery of the Johns Hopkins Hospital has finally grown up.

Elsewhere the Speaker has attempted,—he feels with ill success,—to appraise the value of Dr. Halsted's many contributions to science, and to forecast the place they will occupy when the history of surgery is finally written. Suffice it to say that no one could work under Dr. Halsted for any length of time—as was my privilege for thirty-three years,—without being deeply impressed by his methods of thought and action, his originality, his keen observation and analysis, his insatiable scientific curiosity, his tireless search after truth and his absolute honesty. These characteristics formed the basis of his great success. They are reflected in all of his work, and form the distinguishing marks of the Halsted School of Surgery.

Dr. Halsted was a surgeon in the broadest sense of the term, rather than an operator. The science and the under-lying principles of surgery, rather than the art and the practice of it, commanded his especial interest. He believed the essence of good surgery to be thoroughness in all things pertaining thereto. He was a pioneer in his insistence upon thoroughness in the preparation and training of the prospective surgeon to fit him to meet successfully the great responsibilities of his calling; thoroughness in the routine of physical

examination, history-taking and the diagnostic study of the patient, and in the preparation for the operation. And he believed that the secret of surgery lay in the meticulous attention to every detail, however unimportant apparently, that had to do in any way with the operation before, during and after its performance. Hence it was that one of the striking characteristics of his clinic was the absence of anything that savored of the spectacular. To the uninitiated, he appeared to be a rather slow, anatomical operator, ill at ease before a crowded gallery; but to the surgically elect, his complete grasp of the situation and the perfection of his technique were a joy to behold. His best work was done in the quiet of his laboratory and operating-room, surrounded only by his personally trained and trusted staff of assistants, who were familiar with his methods, thoroughly believed in them, and were enthusiastic in their devotion to him personally and to his ideals of work. Dr. Halsted was not interested in mediocrity and had little patience with it, while, conversely, a brilliant intellect had great attraction for him. Nor was he interested in the man who lacked initiative and waited to be spoon-fed; but the man anxious to learn and to do things, even though he made an occasional mistake, found in him a ready helper and a stimulating influence. He taught by example rather than by precept; he helped a man to help himself. He either trusted a man implicitly or not at all; if he did, he loaded him with responsibility; if he did not, he was given short shrift.

Dr. Halsted was a keen observer. Few phenomena that developed during the course of a physical examination, a surgical operation or the subsequent convalescence, escaped his attention, and when anything out of the ordinary occurred, he was never satisfied until he had found out the reason why. His scientific curiosity was never gratified except by proven facts. His laboratory was his great testing plant. Here he was wont to try out new ideas, to improve upon old ones, to repeat observations made in the operating-room, to confirm or disprove previously formed impressions and theories. He was, in the best sense of the term, an experimental surgeon, always with an open mind. No wonder, then, that he was such a great teacher and contributor to surgical science, or that his clinic was so stimulating and productive. It is a source of great satisfaction to those trained in this School to know that this splendidly planned and appointed

building will bear Dr. Halsted's name, and to feel assured that the mantle of "The Professor," as he was affectionately called by his associates and students, has fallen upon such worthy shoulders as those of Dr. Lewis, one who can be trusted, not only to carry on the best traditions established by the first great surgical master and teacher of this Hospital, but who will, in his turn, contribute others, and thus add new lustre to the name and fame of our beloved Johns Hopkins.

It was indeed most fortunate, for scientific surgery in general and the Johns Hopkins Hospital in particular, that one of Dr. Halsted's ability and attainment should have appeared upon the scene just at the psychological moment, to join the others of that distinguished group in starting the new Hospital along right lines, and in setting the pace for the entire country.

The Johns Hopkins Hospital, where much of Dr. Halsted's best work was done, the scene of his most fruitful labors and greatest triumphs, does well to honor itself in honoring him, by giving his name to this splendid modern surgical building, which we today formally dedicate to the service of humanity and the perpetuation and development of the principles of the science and art of surgery, as enunciated by him during the thirty-three years he so ably filled the chair of surgery in this Institution. These principles, the objects of so much thought and attention by him, and for the dissemination of which he so earnestly strove, are fundamental, and will endure for all time.

BOOK REVIEWS

Procedure in Examination of the Lungs. With especial reference to the diagnosis of tuberculosis. By ARTHUR F. KRAETZER. With a foreword by James Alexander Miller. 8°. 125 Pp. (*Oxford Univ. Press., 1930.*)

This is, in many respects, a unique little volume. Written with the purpose of guiding students to acquire the necessary skill properly to diagnose diseases of the lungs, especially tuberculous disease of those organs, it may be said to accomplish that end.

Wisely, the thesis is emphasized that a clinical diagnosis must be based on a correlation of symptomatology and of evidences of anatomical change; and with rare good judgment the author strives to assure the average student that a knowledge of cardinal facts and a reasonable skill in the utilization of ordinary methods will suffice to disclose clinical faults.

Although the originality of presentation and the informality of diction are refreshing and to a degree captivating, the style is so free as to be to literary form what Communism is to the usual social order. A number of inaccurate statements are made and some controversial points are settled dogmatically with a flourish of the pen, but, on the whole, the book deserves a favorable reception since it will arouse questioning as well as present facts.

C. R. A.

League of Nations. Quarterly Bulletin of the Health Organization. Volume I, No. I. March, 1932. Geneva. 157 Pp. [Single no. $.50, Annual Subscription, $2.00, post free.] (*Publication Dept. League of Nations, Geneva.*)

This Bulletin takes the place of numerous documents formerly issued separately by the League of Nations, as records of international conferences, minutes of committees, annual reports, etc. It is published in English and in French.

This number contains the Resolution of the Conference on Immunization against Diphtheria; Sir George Newman's Medical Education in England; Professor R. Burri's The Milk Supply of North American Cities; R. Gautier's Tropical Pneumonia; A. G. McKendrick's A Second Analytical Review of Reports from Pasteur Institutes on the Results of Anti-Rabies Treatment; The Floods of China, a report by the Medical Director. The last article is from an epidemiological standpoint.

This periodical will be of the greatest interest, especially to hygiene and public health officers.

E. S. T. M.

The Pathology of Internal Diseases. By WILLIAM BOYD. Illustrated. With 298 engravings. 8°. 888 Pp. $10.00. (*Lea and Febiger, Philadelphia, 1931.*)

Most textbooks of medicine have a brief paragraph under each disease heading on morbid anatomy, and most textbooks of pathology have vague references to signs and symptoms. In this volume, Doctor Boyd has endeavored to correlate as far as possible the present data of pathological physiology and pathological anatomy with the signs and symptoms recorded by clinicians. It is perhaps more a textbook of medicine based on the mechanism of disease than a textbook of pathology, but no similar approach with the emphasis on correlation has been as satisfactorily done before within the limits of one volume. Whether the interpretations and discussions here will hold, only further investigations will tell, but Dr. Boyd has at least prepared an unusually readable volume and even the most critical will condone, if not approve, his efforts at correlation.

D. B. R.

The Treatment of Asthma. By A. H. DOUTHWAITE, M.D., F.R.C.P. [Lond.] 18°. 158 Pp. (*William Wood & Co., New York.*)

This book is quite elementary and there is considerable repetition in the different chapters. It deals with the diagnosis and the symptomatic treatment of asthmatic patients. The chapter on desensitization is incomplete and might mislead a student rather than help him in the modern methods of this procedure. The bibliography is incomplete as far as American literature is concerned; in fact many of the more recent European publications have also been omitted.

L. N. G.

The Clinical Examination of the Nervous System. By G. H. MONRAD-KROHN, M.D., F.R.C.P. With a Foreword by T. Grainger Stewart, M.D., F.R.C.P. 5th Edition. 19°. 222 Pp. (*Paul B. Hoeber, Inc., New York, 1930.*)

This is a very useful little book which compares favorably with other publications of a similar type. The author not only gives a good description of the common clinical and laboratory tests, but makes clear the indications and significance of each one. The studies which should be made as a routine are distinguished from those which are indicated only in special instances. The book shows evidences of sound judgment and may be warmly recommended to students and practitioners.

F. R. F.

Cytology and Cellular Pathology of the Nervous System. Edited by WILDER PENFIELD. 3 vols. 1252 Pp. 886 illusts. $10.00 per volume. (*Paul B. Hoeber, Inc., New York, 1932.*)

These volumes cover a field of literature too vast to explore unaided. The list of 26 contributors including such workers as Bielschowsky, Hortega, Kappers,

Nageotte, Penfield and Weed gives a true impression of the scientific calibre of the work.

Each section is a monograph treating some special phase of neurocytology in the systematic manner necessary for an introduction, and at the same time critically discussing current work and unsolved problems. The direct study of living cells and improved staining methods have made possible complete revision of certain phases of elementary cellular morphology and physiology. In many instances the author bases his account on personal convictions derived from first-hand investigations, instead of attempting the impersonal neutral presentation expected in textbooks. The reader, however, is adequately directed to other important views through extensive bibliographies, international in scope.

The subject matter includes nerve cells and the associated cells which form the nervous system with its coverings and blood vasculature. The behavior of each of these tissues in health and in response to injury is systematically described. Within this province the work is exhaustive, whereas disease entities receive little attention.

These volumes are a worthy memorial to the spirit of scientific investigation exemplified in the histological work of Ramón y Cajal. Their wealth of information should be accessible to every student of neurology.

W. L. S.

Alimentary Anaphylaxis. [*Gastro-intestinal Food Allergy.*] By GUY LAROCHE, CHARLES RICHET FILS AND FRANÇOIS SAINT-GIRONS. Foreword by Professor Charles Richet. Translated by Mildred P. and Albert H. Rowe. 18°. 139 Pp. $2.00. (*Univ. of California Press, Berkeley, Calif., 1930.*)

This monograph, consisting of seven chapters, gives a brief discussion of the problem of food allergy as related to gastro-intestinal symptoms. It should certainly be read by those interested in hypersensitivity but inasmuch as more conservative authorities still do not consider alimentary anaphylaxis as a distinct entity, the conclusions which are drawn should not be accepted too seriously until further investigations have been made. Numerous cases compiled by the authors are presented in this volume and they are most interesting instances of good hypersensitivity. Pathogenesis, diagnosis and treatment are dealt with briefly and the biography is extensive; no reference is made to the work which has been done in England or in the United States.

L. N. G.

The Physician of the Dance of Death. By ALFRED SCOTT WARTHIN, Ph.D., M.D., LL.D. 1931. 92 illust. 142 pp. (*Paul B. Hoeber Inc., New York.*)

Ever since 1424, and through the ages of the Renaissance and the Reformation, the fear of death has intrigued the world. It was the essential spirit of the day, that no matter what was the nature of the malady, the physician as well as the patient had to come face to face with death, combat it and then flee from it. It

followed the physician and conspired with and against him. It was a gruesome picture which finally, in the XIXth century, took hold of the world through the caricatures of Cruikshank, Rowlandson and others. The modern "Totentanz" does not invade our civilization in the diffuse manner which characterized its approach in the past, but comes only in moments of misery when death is your friend and leads you away to rest. Warthin completely covers this story in a most interesting and gripping fashion, imbuing it with his own philosophy. The book is extremely well written, the descriptions and the mental states of individuals very graciously penned. Perhaps its only fault is the emphasis on the imitators of Holbein, a purely academic interest, rather than on the works of Holbein himself. Only one Holbein illustration is shown. Holbein was a leading spirit, and gave to the Dance of Death hundreds of forms in his drawings which were to have their lasting influence. As usual, Paul B. Hoeber has taken the trouble of good paper, good type, and excellent illustrative reproduction. To anyone interested in medicine, the book will prove most illuminating; to anyone concerned with pathology it should revive the tender memory of Warthin and his lifelong interest in the "Totentanz."

M. P.

Behavior Aspects of Child Conduct. By ESTHER LORING RICHARDS, B.A., M.D., D.Sc. 299 pp. 20°. $2.50. (*The Macmillan Co., New York.*)

This interesting book comprises a series of lectures delivered to a child-study association group. It deals with the management and treatment of conditions commonly ascribed to the "badness" or "nerves" of childhood. The author writes with a directness of approach and concrete description which is a welcome relief from the abstruse and, usually, maudlin and meaningless terminology of many books dealing with such subjects.

The book is unreservedly recommended to all interested in abnormal behavior of children and particularly to teachers or others professionally in contact with the manifold problems encountered in dealing with any group, including so-called normal children. The clinician and surgeon, too, to avoid errors due to a failure to differentiate psychic from physical ailments, will profit from the wise experiences of Dr. Richards as detailed in her book.

A. G.

Operative Obstetrics on the Manikin for Students & Practitioners. By CHARLES B. REED. 1931. 314 pp. $4.00. (*P. Blakiston's Son & Co., Phila.*)

This is a valuable complement to our standard American text-books of Obstetrics. It is up to date and comprises all that is needed for the instruction of students, and also those engaged in post-graduate work. The illustrations are, in a large measure, taken from the best known German and English books on the same subject and serve to enrich the worth of the description of the various operations.

This book fills a gap in the American Obstetrical Literature.

J. H.